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ELECTROCARDIOGRAPHIC CHANGES IN PERICARDITIS ASSOCIATED WITH UREMIA

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ONE of the responsibilities of the present-day physician is that of caring for the patient who has uremia. More of these patients now are seeking medical advice, and the condition demands broader and more accurate knowledge than heretofore. During the last few years, closer observation of these patients in the hospital has led to the more frequent recognition of pericarditis.[1-6] Different investigators have suggested that serial electrocardiograms taken during the course of pericarditis[7, 8] should give needed information in regard to typical abnormalities and that a more accurate appraisal of the significance of these abnormalities should be made.

The following report consists of clinical, chemical, serial electrocardiographic, and pathologic observations in three cases of severe chronic renal insufficiency in which recognizable pericarditis developed while the patients were under our care. These cases presented a unique opportunity for an intensive study of uremic pericarditis.

REPORT OF CASES

CASE 1.—The patient, a white youth, was 17 years of age when he first registered at the Mayo Clinic, Oct. 24, 1939, approximately four years before the terminal illness during which pericarditis developed. He had contracted measles and mumps in early childhood. He had undergone tonsillectomy when he was 3 years of age. At 7 years he had scarlet fever, from which he recovered completely. In March, 1939, when the patient was 17 years of age, he developed a septic sore throat with fever and remained in bed for four days. There had been no definite sequelae. In the family history no significant facts were found with regard to the patient's illness.

In September, 1939, edema of feet and legs and some puffiness of the eyelids developed insidiously, and gradually increased. Albuminuria, hematuria, and cylindruria were found

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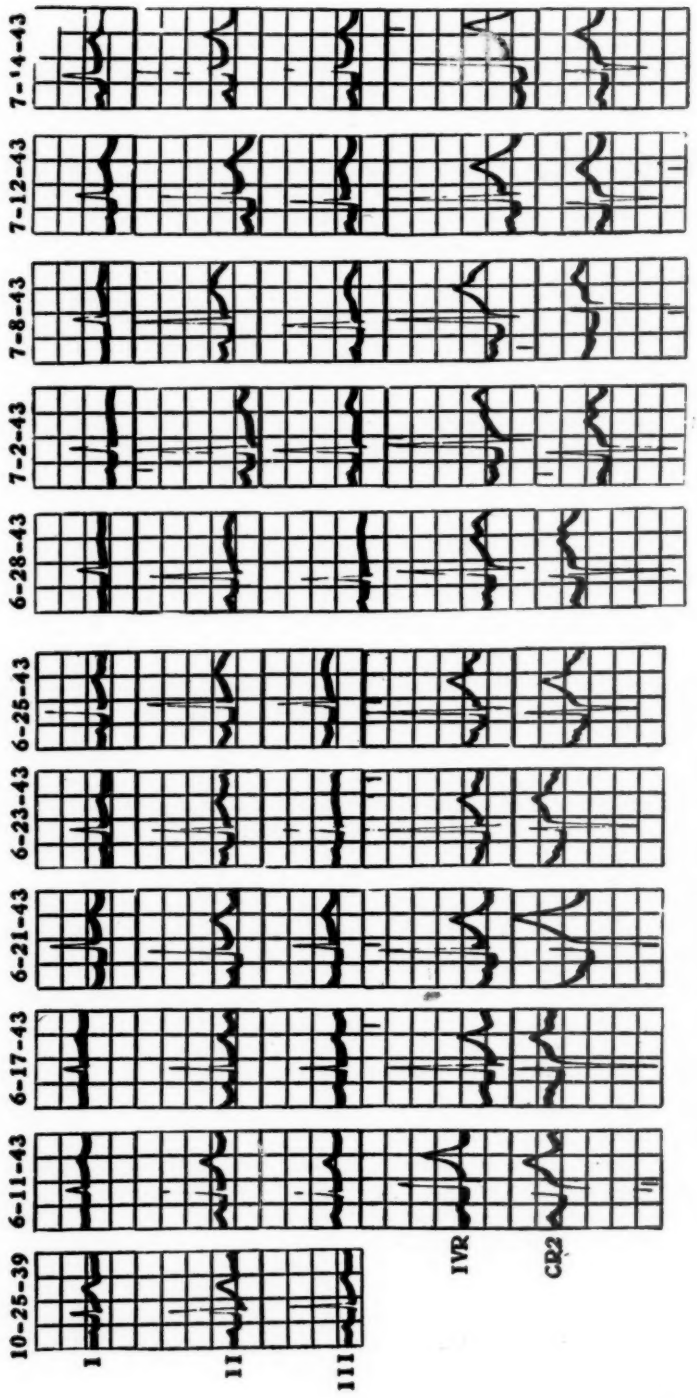

Fig. 1.—(Case 1.) In this series of electrocardiograms, changes of a type observed in pericarditis reach a maximum on June 21, regress, and then recur. They are still present in the last tracing taken before the patient's death.

on urinalysis at that time. The patient had been put to bed and in three weeks the edema had subsided although albuminuria persisted.

Physical examination on admission to the clinic on Oct. 24, 1939, revealed that the patient was 69½ inches (176.5 cm.) tall and weighed 146 pounds (66.2 kg.). There was slight edema of the eyelids and moderate edema of the dependent portions of the body. The lungs were clear, and there was no gross enlargement of the heart. With the ophthalmoscope a single small hemorrhage in the right retina was seen. The initial blood pressure was 170/90. Several routine urinalyses revealed albumin, Grade 3 to 4 (on a grading basis of 1 to 4, in which 1 represents the least amount and 4 represents the most amount); no reducing substances; some hyaline and granular casts; erythrocytes, Grade 2 to 3; and leucocytes, Grade 0 to 4. An electrocardiogram taken on October 25 revealed no significant variations from the normal (Fig. 1). Studies of the blood revealed mild secondary anemia, negative results of the flocculation test for syphilis, increased concentrations of urea (48 mg. per 100 c.c.) and cholesterol (287 mg.), and distinct hypoproteinemia (Table I). The standard urea clearance was reduced to 15 c.c. of blood cleared per minute. A diagnosis of early chronic glomerulonephritis was made and the patient was hospitalized. During the two weeks the patient was in the hospital the edema disappeared and he lost 17 pounds (7.7 kg.). Treatment consisted of a diet low in sodium chloride, which contained 2,000 calories and 80 Gm. of protein. The intake of fluids was limited to 1,500 c.c. per day. The diuretics, potassium nitrate, theobromine, and aminophylline, were given. Also 90 Gm. of acacia in a 6 per cent solution were injected intravenously.

The patient's second admission was on July 10, 1940. His general condition was good. The only abnormality was a trace of edema above both ankles. The blood pressure was 160/90. Urinalysis revealed findings similar to those on first admission. There was definite evidence of renal insufficiency; for example, the serum sulfate had increased to 7.3 mg. in 100 c.c. (Table I).

A year later, on Nov. 24, 1941, the patient returned to the clinic. He had attended school regularly in the interim. He had no edema, the blood pressure was 150/80, and the ophthalmoscopic findings in the retina were normal. The secondary anemia was more severe than on prevoius visits and renal insufficiency was more marked as evidenced by the standard urea clearance which was reduced to 6 cubic centimeters. Urinary findings were similar to those on previous visits. At this time the patient was given a transfusion of 500 c.c. of blood.

For the next year the patient had few untoward symptoms. However, during the winter of 1942 and 1943 the anemia became difficult to control and he was given nine transfusions of blood. His appetite became poor and in the six months before his last admission he occasionally vomited.

On the fourth and last admission, June 9, 1943, the patient was distinctly anemic. He was hospitalized at once. His breath had a uremic odor. The heart was not greatly enlarged. A soft systolic murmur was heard over the pulmonary region. However, there was no edema, and no retinitis was demonstrated on ophthalmoscopic examination. The blood pressure had risen to 175/115. Quantitative estimations of the protein in the urine revealed that the amount excreted varied from 1.14 to 1.93 Gm. in 100 c.c. of urine, and the total amount excreted in twenty-four hours varied from 3.5 to 16 grams. In spite of this considerable daily loss of protein in the urine, the serum protein and albumin fraction were at the lower limits of normal concentrations (Table I). Blood studies revealed distinct secondary anemia and marked azotemia. The concentration of blood urea was 342 mg. and of creatinine was 28 milligrams.

In the thirty-seven days the patient was under observation, the course was typical of terminal uremia secondary to chronic glomerulonephritis. Twenty-four hours after the patient was admitted to the hospital several general convulsions developed. Each was of short duration. Four days later, June 14, examination of the mouth revealed a white membranous exudate beneath the tongue, having the characteristics of so-called uremic frost. The next evening the patient had a general convulsion which lasted for ten minutes. On June 16, for the first time, a faint precordial to-and-fro friction rub was heard in the second left intercostal space. This rub was not heard thereafter until June 21 when a loud friction rub became

TABLE I. DATA ON BLOOD IN CASE 1

DATE	WHOLE BLOOD			BLOOD SERUM								BLOOD PLASMA			
	HEMOGLOBIN (GM. IN 100 C.C.)	UREA (MG. IN 100 C.C.)	CREATININE (MG. IN 100 C.C.)	PROTEIN (GM. IN 100 C.C.)	ALBUMIN (GM. IN 100 C.C.)	ALBUMIN-GLOBULIN RATIO	SULFATE (MG. IN 100 C.C.)	CALCIUM (MG. IN 100 C.C.)	PHOSPHORUS (MG. IN 100 C.C.)	SODIUM (MG. IN 100 C.C.)	POTASSIUM (MG. IN 100 C.C.)	CHLORIDE (MG. IN 100 C.C.)	CARBON DIOXIDE COMBINING POWER (VOLUMES IN 100 C.C.)	CHOLESTEROL (MG. IN 100 C.C.)	ELECTROCARDIOGRAM
10/25/39	10.8	48		4.0	2.5	1.7/1								287	ECG
10/26/39												621	54		
10/27/39							5.1								
10/30/39		38													
11/ 7/39		46													
7/20/40	11.6	42		4.4	2.8	1.7/1	7.3					617			
10/28/40	11.4	60		4.8	2.9	1.6/1	7.3								
11/25/41	8.9	122	6.4	5.2	3.4	1.9/1	9.7								
12/30/41	9.6	132	7.2									604	50		
1/ 2/42	11.6														
6/10/43	10.3	342	28	6.1	3.9	1.8/1	37	8.6	15		22.2	540	38		ECG 6-11
6/16/43		370	30									441	62		
6/17/43*		358	29				30		20	328	16.8				ECG
6/18/43							25	6.2			17.0				
6/21/43		380	34				32				17.9	380	43		ECG
6/23/43		399	32				27				20.6				ECG
6/25/43	8.0	357	28								18.5	369	61		ECG
6/28/43		372	28				25				15.6				ECG
7/ 2/43		354	28				29	6.3	7	288	14.8	373	50		ECG
7/ 6/43		346	24				34		8		13.5	380	50	†	ECG
7/ 8/43*‡	5.3	372	28	5.2	3.1	1.5/1	24	6.5	12.5	285	13.6	330	48	256	ECG
7/12/43§	4.7	468	34				34		13		16.5	320	38		ECG
7/13/43		498	34								20.7				
7/14/43		504	30				47		17	279	21.6	290	43		ECG
7/15/43		558	34				61		20	273	23.6	297	43		
11:00 A.M.															
2:55 P.M.		Patient died													

*Serum magnesium on June 17, 3.5 mg., and on July 8, 1.2 mg. in 100 c.c., respectively.

†Plasma cholesterol esters, 139 mg.; lecithin, 245 mg.; total fatty acids, 662 mg.; and total lipoids, 918 mg. in 100 cubic centimeters.

‡Blood culture: no growth in five days.

§Blood sugar, 106 mg. in 100 c.c.; blood uric acid, 14.8 mg. in 100 cubic centimeters.

audible and continued to be heard until June 24. Electrocardiographic tracings taken in the course of the first examination in October, 1939, and on June 11 and 17, 1943, in the first week of the last stay in the hospital, were not indicative of pericarditis (Fig. 1). However, on June 21, when the loud rub over the precordium developed, electrocardiographic tracings taken in the morning showed significant elevation of the RS-T segment in all three standard leads and in precordial Leads CR_2 and 1VR. In the period from June 17 to 23, the patient's temperature rose each day to 99° F. or higher, and on June 18 it rose to 101° F. It is worthy of note that subsequently from June 25 to July 2 no pericardial friction rub was audible, the patient's temperature was normal, and the electrocardiographic changes diminished in magnitude. In the tracing taken on June 28 the RS-T segments were isoelectric in all leads except in Lead CR_2. The amplitude of the T waves especially in the standard leads was low in comparison to the height of this deflection in electrocardiograms taken prior to the episode of pericarditis (Fig. 1).

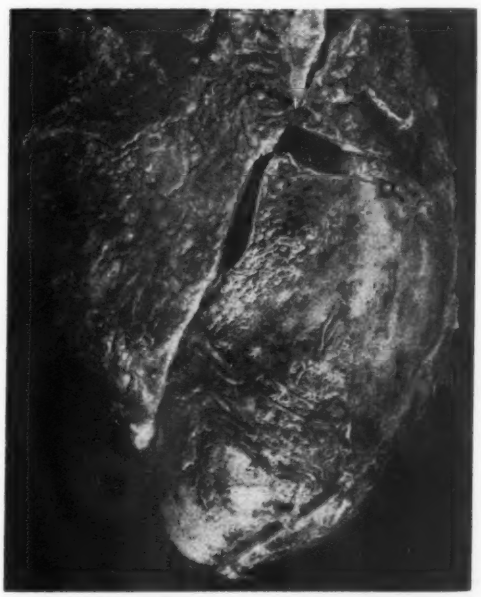

Fig. 2.—(Case 1.) Sanguinofibrinous pericarditis with fibrous adhesions.

On July 8, the friction rub recurred and persisted until the patient died on July 15. A culture of the blood taken on July 8 failed to show any growth over a period of five days. From July 9 to 15, inclusive, the patient's temperature rose to as much as 100.2° F. In the electrocardiogram made on July 8, elevation of the RS-T segment reappeared in the standard leads and precordial Lead 1VR. Throughout the last seven days of the patient's life the friction rub was detectable and in electrocardiograms taken in this period the RS-T segment remained elevated (Fig. 1).

It is of interest that, in spite of the extreme grade of renal impairment, oliguria developed only during the last few days of life. The continued excretion of a considerable volume of urine was at least partly due to the intravenous injection of glucose solutions.

Blood was withdrawn from the vein of the arm of the patient on July 8 and analyses of the concentration of several ions in the plasma and serum were made. The results given in Table II reveal a low total ionic concentration and a preponderance of basic ions. These findings, in addition to carbon dioxide combining power in the plasma of 48 volumes per cent, support the viewpoint that even in marked chronic azotemia, as it occurred in this patient, acidosis need not necessarily be continually present.

On July 15 bilateral parotitis was present. The patient periodically lapsed into a semicomatose condition and died at 2:55 P.M.

Necropsy.—There was moderate emaciation. Two decubital ulcers, each 1 cm. in diameter, were present on the right buttock. There were 200 c.c. of blood-tinged fluid in the peritoneal cavity. The pericardial sac measured 15 cm. transversely and contained approximately 200 c.c. of bloody fluid. The epicardium and inner surfaces of the pericardial sac were covered by a thick hemorrhagic exudate (Fig. 2).

The heart weighed 330 grams (normal, 265 grams). A few dense fibrinous adhesions extended from the epicardium to the pericardial surface.

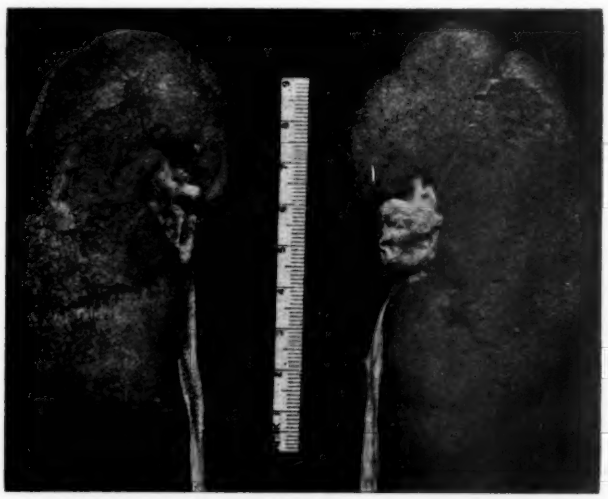

Fig. 3.—(Case 1.) Chronic glomerulonephritis with atrophy of the left kidney.

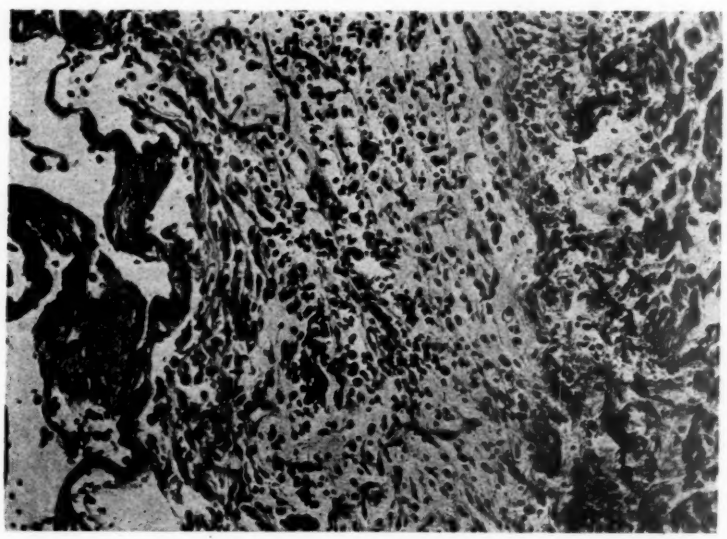

Fig. 4.—(Case 1.) Pericarditis. Note organization of the fibrinous exudate at the left (hematoxylin and eosin, ×120).

The lungs, except the right lower lobe which was slightly increased in consistency, appeared to be normal. The cut surface of the lower lobe of the right lung was dark red.

The right kidney weighed 130 grams (normal). The capsule was stripped with great difficulty from a granular yellowish surface (Fig. 3). The cut surface was yellowish and the markings were indistinct. The cortex measured 3 mm. and the medulla measured 20 millimeters. The left kidney weighed 88 grams. Aside from its smaller size it resembled the right kidney in appearance.

Histologic Examination.—The parietal and visceral pericardia were covered by a fibrinous hemorrhagic exudate containing a few mononuclear cells. Active organization of this exudate by fibroblasts was observed (Fig. 4). No lesions were observed in the myocardium.

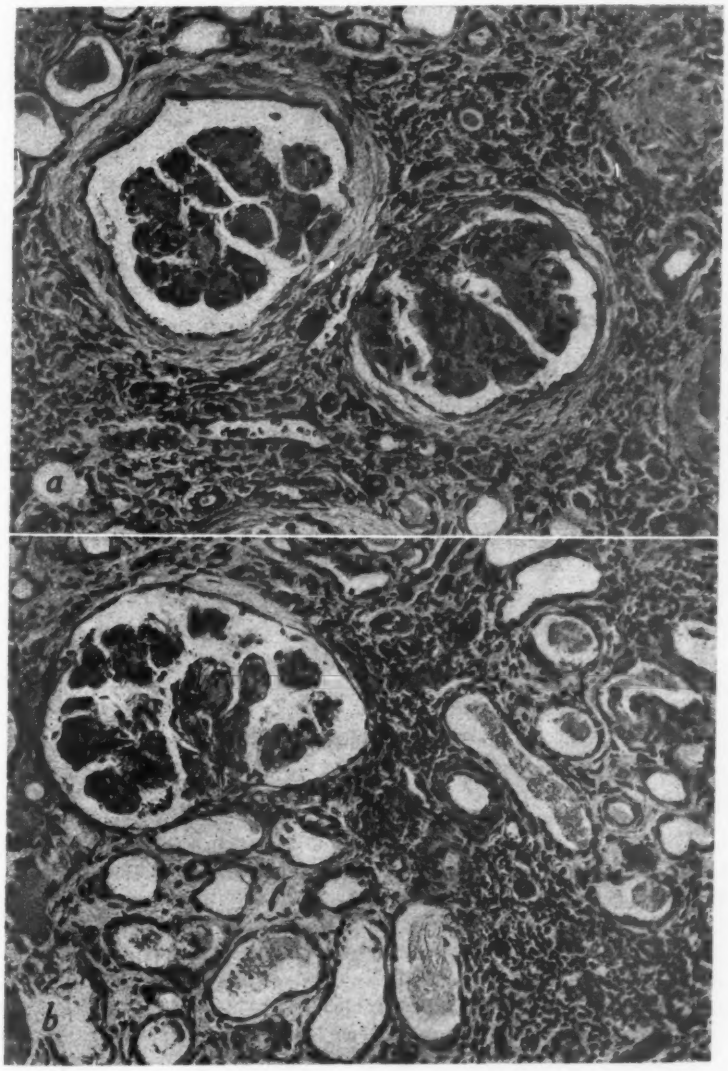

Fig. 5.—(Case 1.) Kidney. *a*, Proliferation of endothelial cells and hyalinization of glomerular tufts. Resemblance to intercapillary glomerulosclerosis may be noted (hematoxylin and eosin, ×145). *b*, Same changes in glomerulus and thickening of wall of small arteriole as shown in *a*. Tubules are dilated (hematoxylin and eosin, ×125).

TABLE II. DISTRIBUTION OF ELECTROLYTES IN BLOOD PLASMA AND SERUM IN CASE 1*

BASE	MG. IN 100 C.C.	MEQ. IN 1,000 C.C.	ACID	MG. IN 100 C.C.	MEQ. IN 1,000 C.C.
Sodium	285	124	Chlorides†	198	56.4
Potassium	13.6	3.5	Bicarbonate	48‡	21.5
Calcium	6.5	3.2	Protein	5.2§	12.5
Magnesium	1.2	1.0	Sulfates	24	5.0
Total Meq.		131.7	Phosphates	12.5	8.0
			Total Meq.		103.4

*Blood withdrawn July 8, 1943.
†Chlorides estimated as chlorine.
‡Bicarbonate estimated from carbon dioxide combining power.
§Gram in 100 c.c. of serum. Base milliequivalents per liter bound by protein = 0.243 times grams of protein per liter.

In sections of the right lower lobe of the lung the alveoli were filled with serum and fibrinopurulent exudate.

In sections of the kidneys no normal glomeruli could be observed. About 60 per cent of the glomeruli were fibrotic, hyalinized, and obviously functionless structures. The remaining glomeruli revealed evidence of injury of varying degrees. Many of them were hypertrophied. The most constant change was endothelial proliferation of the glomerular tufts. Most of the capillaries were partially or completely blocked by this abnormal accumulation of endothelial cells. In some of these glomeruli, hyaline globular structures were present in the peripheral portions of the tufts (Fig. 5, *a* and *b*). These hyaline structures were identical in appearance to the lesions described in the kidney in Kimmelstiel-Wilson disease (intercapillary glomerulosclerosis[9]). Adhesions between the glomerular tuft and the capsule, and pericapsular fibrosis were other changes frequently observed. Most of the tubules were atrophied and collapsed. Collections of lymphocytes were present in the interstitial tissue. A few tubules were dilated and contained casts of acidophilic albuminous material and red blood cells.

The large arteries appeared normal. The arterioles revealed moderate hypertrophy of the media but rarely any intimal hyalinization.

The following diagnoses were made: (1) chronic glomerulonephritis with atrophy of the left kidney and uremia (clinical); (2) chronic fibrinohemorrhagic pericarditis; (3) hypertrophy of heart (hypertension), and (4) early bronchopneumonia in the lower lobe of the right lung.

CASE 2.—The patient, a married white woman, 35 years of age, was admitted to the Mayo Clinic on Jan. 11, 1944, and was hospitalized immediately. She was suffering from uremia presumably due to chronic glomerulonephritis. She complained chiefly of dyspnea, edema of the legs, nausea, and vomiting. The family history revealed that her mother had Bright's disease and that one brother had high blood pressure. The patient had been married for seventeen years and was the mother of two healthy children. She had scarlet fever at 4 years of age and she underwent tonsillectomy at the age of 12 years. During the patient's first pregnancy, when she was 18 years of age, albuminuria was found and this had persisted since that time. Three years before admission the urine contained casts, blood, and pus, in addition to albumin. Her systolic blood pressure was 190 millimeters. Six weeks before admission, dyspnea with cough, dependent edema, some blurring of vision, nausea, and vomiting developed. Her systolic blood pressure was found to be more than 200 millimeters.

On physical examination at the clinic, the patient was 66¼ inches (168.3 cm.) tall and weighed 113½ pounds (51.5 kg.), and the blood pressure was 240/140. She was anemic. Numerous moist râles were heard over the bases of the lungs. On percussion the heart was found to be slightly enlarged, measuring 2.5 by 12.5 centimeters. The second aortic sound was accentuated, but no murmurs or rubs were audible. The liver and spleen could be felt at the costal margin. There was edema, Grade 1, of the lower part of the legs. On ophthalmoscopic examination the retinas were anemic, the optic discs were edematous up to 1 diopter, and

there were scattered cotton-wool exudates and hemorrhages. The retinal findings were those of an acute angiospastic retinitis. Twenty routine urinalyses revealed albumin, Grade 2 to 4, and no reducing substances. In the sediment, erythrocytes and leucocytes, Grade 1, were found periodically. The finding of casts was not recorded. An accurate quantitative estimation of protein revealed 0.3 Gm. in 100 c.c. of urine. Blood studies indicated secondary anemia (hemoglobin, 9.1 Gm. in 100 c.c.); erythrocytes 3,100,000 per cubic millimeter, and leucocytes 4,300. The result of the flocculation test on the serum was negative for syphilis. The blood urea was 238 mg. and the serum sulfate was 26.3 mg. in 100 c.c. (Table III). These levels are indicative of severe azotemia. A roentgenogram of the thorax showed an enlarged heart shadow and a small effusion in the right pleural cavity. An electrocardiogram taken on January 12 showed nothing diagnostic of pericarditis or myocardial disease (Fig. 6).

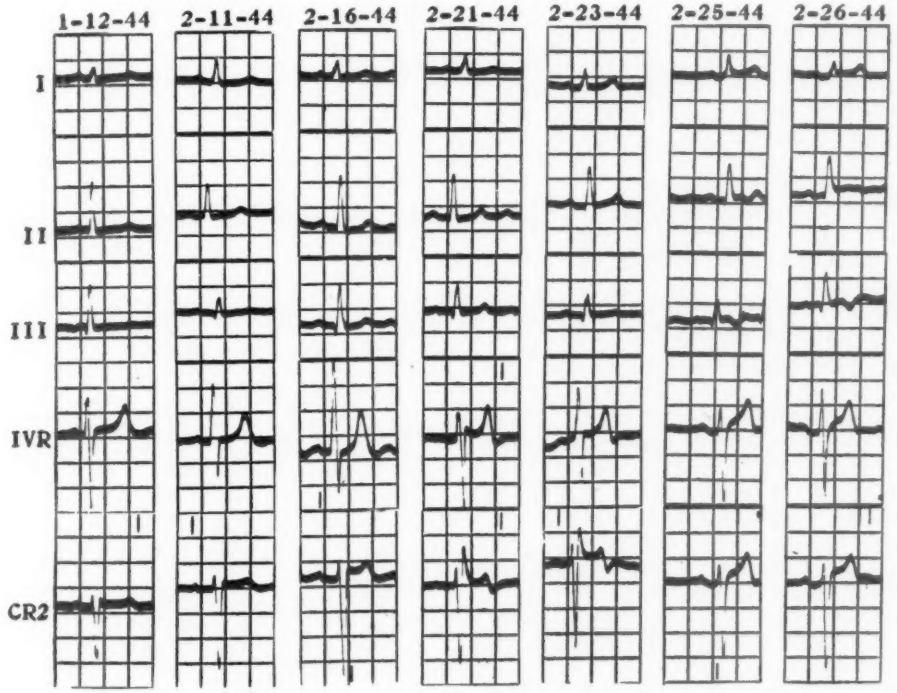

Fig. 6.—(Case 2.) Changes of a type observed in pericarditis never were present in more than minimal degree in this series of electrocardiograms. In the tracing taken on February 16, the RS-T segment in precordial Lead CR_2 is slightly elevated. Changes in this lead attain their greatest degree on February 23. Slight elevation of the RS-T segments in the standard leads appeared in the electrocardiogram on the same day and persisted throughout the remaining tracings.

The course of the patient's illness from Jan. 11 to Feb. 27, 1944, was typical of the terminal uremic state seen in chronic diffuse nephritis. The blood urea and creatinine gradually rose to 564 mg. and 23.5 mg. in 100 c.c., respectively, and the carbon dioxide combining power of the plasma decreased to 24 volumes per cent. Distinct oliguria did not develop until the last four days of the patient's life. From January 11 to February 11, the patient's condition changed little and at times she was fairly comfortable. Treatment included intravenous injections of glucose solutions and a transfusion of 500 c.c. of blood on January 26. On February 11, a few moist râles were audible over the bases of the lungs, but no change occurred in the region over the heart. The electrocardiogram was unchanged from that taken on January 12 (Fig. 6). On February 15, the patient became mildly confused and had some hallucinations. At times during the next day, February 16, twitching movements of the ex-

TABLE III. DATA ON BLOOD IN CASE 2

DATE, 1944	WHOLE BLOOD			BLOOD SERUM				BLOOD PLASMA		ELECTRO-CARDIOGRAM
	HEMOGLOBIN (GM. IN 100 C.C.)	UREA (MG. IN 100 C.C.)	CREATININE (MG. IN 100 C.C.)	POTASSIUM (MG. IN 100 C.C.)	CALCIUM (MG. IN 100 C.C.)	PHOSPHORUS (MG. IN 100 C.C.)	SULFATE (MG. IN 100 C.C.)	CHLORIDE (MG. IN 100 C.C.)	CARBON DIOXIDE COMBINING POWER (VOLUMES IN 100 C.C.)	
1/12	9.1	238					26.3			ECG
1/14								557	48	
1/18		226	10.4	21.0						
1/19		216	11.0							
1/28	9.6	220	12.8				21.1			
2/2*		204	13.4	25.4				544	37	ECG
2/11		204	16.2	21.6	9.2	8.6		451	44	ECG
2/14†		240	16.8	19.0		10.6	18.2	449	47	ECG
2/16		236	16.2	16.8						ECG
2/18‡	8.4	272	18.3	20.6				402	38	ECG
2/21		366	19.6	23.9						ECG
2/23		426	23.2	22.9				462	24	ECG
2/25		492	23.0	24.1	7.8	16.6		453	27	ECG
2/26		564	23.5	25.6				455	24	ECG
2/27		Patient died								

*Serum protein, 5.5 Gm. in 100 cubic centimeters.

†Serum sodium, 262 mg. in 100 cubic centimeters.

‡Serum protein, 4.9 Gm.; serum albumin, 3.6 Gm.; albumin-globulin ratio, 2.7/1.0; plasma cholesterol, 234 mg.; cholesterol esters, 160 mg.; lecithin, 262 mg.; total fatty acids, 436 mg.; total lipoids, 670 mg. in 100 cubic centimeters.

tremities and signs of bilateral hydrothorax developed. Edema, Grade 3, of the lower part of the back was also present. An electrocardiogram showed an increase in the height of the T wave in Lead IVR and a sharpening of the apex of this wave; the RS-T segment in Lead CR_4 was slightly elevated (Fig. 6). The patient's temperature was normal from January 29 to February 18, with the exception of February 16 when it reached 99.4° F.; however, from February 18 to February 23, it rose to 100° to 100.6° F. On February 21, so-called uremic frost covered the patient's tongue and the mucous membrane of the oral cavity and, for the first time, a precordial friction rub was heard. The electrocardiogram on the same day revealed that elevation of the RS-T segment in Lead CR_2 had increased and a slight elevation of this segment had appeared in Lead IVR. The friction rub continued to be audible throughout the remaining six days of the patient's life. In the electrocardiogram taken on February 23 (Fig. 6), a slight elevation of the RS-T segment in Leads I and II had appeared, and this feature was retained in the subsequent tracings taken on February 25 and February 26. However, the segmental elevation in the precordial leads disappeared almost completely in the last two electrocardiograms of February 25 and 26 (Fig. 6). The patient gradually became weaker and more drowsy and, on February 26, her blood pressure fell to 130/60, and the carbon dioxide combining power of the plasma decreased to 24 volumes per cent, indicating definite acidosis. On February 27, the patient was very drowsy, her blood pressure fell to 90/50, her temperature fell to 97.4° F., and she died at 9:25 P.M.

Fig. 7.—(Case 2.) Fibrinopurulent pericarditis.

Necropsy.—The peritoneal cavity contained 1,000 c.c. of clear yellow fluid and each pleural cavity contained 1,500 cubic centimeters. The pericardial sac measured 14 cm. transversely and contained 250 c.c. of yellow fibrinopurulent exudate.

The heart weighed 403 grams (normal, 234 grams). The entire epicardium was covered by a shaggy fibrinopurulent exudate which varied in thickness and was most prominent at the apex on the anterior surface (Fig. 7). There was a subendocardial hemorrhage in the papillary muscle of the left ventricle. The coronary arteriosclerosis was Graded 1, and there were no thrombi.

At the apex of the upper lobe of the left lung a brown wedge-shaped region of increased consistency measured approximately 2 by 2 cm.; it had the appearance of an infarct. Aside from severe atelectasis of the lower lobes of both lungs, no other lesions were observed in the lungs.

The right kidney measured 6 by 3.5 by 2 cm. and weighed 28 grams. The capsule was stripped with great difficulty from a granular and scarred surface. The cut surface was light brown and the markings were indistinct. The left kidney measured 6 by 3.5 by 1.5 cm. and weighed 24 grams. It had the same appearance as the right kidney (Fig. 8).

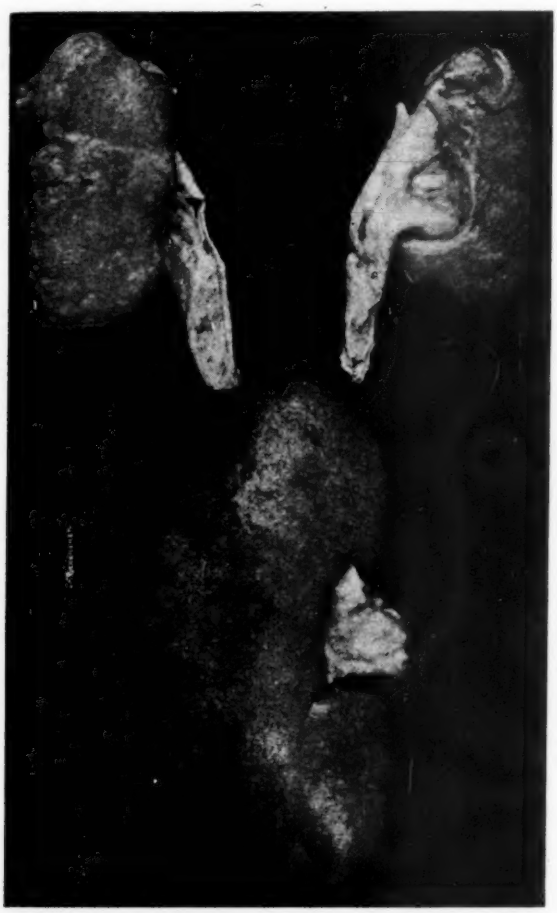

Fig. 8.—(Case 2.) Severe pyelonephritic atrophy of kidneys. Normal kidney below for comparison.

The mucosa of the bladder was congested moderately and there was severe bullous edema. The mucosa of the vagina was ulcerated and covered by a hemorrhagic purulent exudate which extended into the cervix. There were multiple small petechial hemorrhages on the surface of both ovaries.

Histologic Examination.—The parietal and visceral layers of the pericardium were covered by a fibrinous exudate which contained many polymorphonuclear cells and numerous colonies of microorganisms. These had the appearance of cocci. Numerous fibroblasts were growing into the fibrinous exudate from the epicardium (Fig. 9). No lesions were observed

in the myocardium. Sections of the upper lobe of the left lung revealed a recent infarct. There was moderate fatty metamorphosis in the liver.

In sections of the kidneys most of the glomeruli were fibrotic, hyalinized structures which appeared completely functionless (Fig. 10, *a*). A few glomeruli appeared normal but were greatly hypertrophied. Others presented thickening of the basement membranes of the capillary loops and focal hyalinization. The tubules were for the most part severely atrophied and collapsed. A few tubules in association with fairly normal glomeruli were dilated and contained acidophilic hyaline casts. In some regions numbers of tremendously dilated tubules lined by flattened epithelium and filled with acidophilic hyaline casts could be observed (Fig. 10, *b*). No glomeruli were visible in these areas. In sections of the left kidney there was suppurative interstitial nephritis with small abscesses (Fig. 10, *c*). Some of the tubules contained a purulent exudate. The small arterioles of the kidney were the seat of severe hyaline intimal thickening. There was moderate medial hypertrophy of the larger arterioles and arteries. Collagenous intimal thickening and reduplication of the elastic lamina were also observed (Fig. 10, *b*).

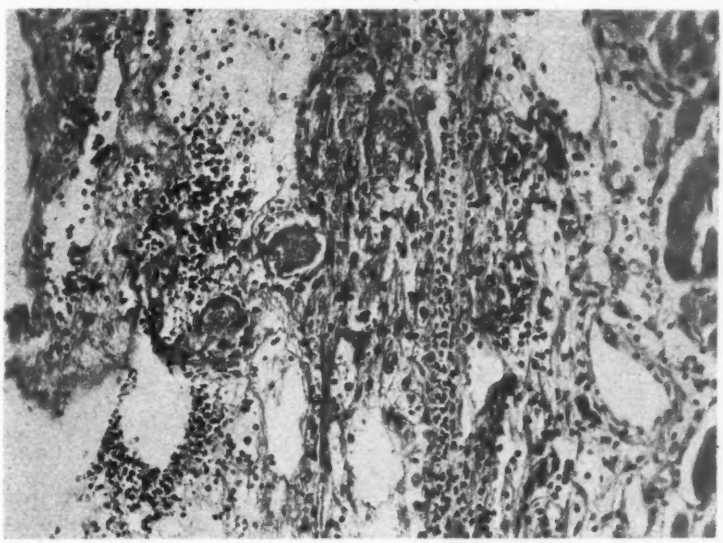

Fig. 9.—(Case 2.) Pericardium. Note organization of the fibrinopurulent exudate by fibroblasts (hematoxylin and eosin, ×140).

Sections of the bladder revealed severe edema of the submucosa with the presence of many large mononuclear cells. In sections of the vagina there was evidence of recent thrombosis of small arteries with intense congestion of submucosa and ulceration of the epithelial surface.

The following diagnoses were made: (1) chronic pyelonephritis (interstitial nephritis) with atrophy of kidneys (total weight, 52 grams; normal, 234 grams) and uremia (clinical); (2) hypertrophy of heart (hypertension); (3) fibrinopurulent pericarditis; (4) bilateral hydrothorax and ascites; (5) infarct upper lobe of left lung; (6) bullous edema of bladder; and (7) ulcerative vaginitis and cervicitis.

CASE 3.—The patient, a white woman, was 37 years of age, a housewife, and mother of two healthy children when admitted to the Mayo Clinic. She was hospitalized immediately on Feb. 23, 1944. Nothing in the family history appeared to be significant with regard to her present illness. The important events in her past history were the development of urinary infection in the course of her first pregnancy in 1932; right tubal pregnancy for which right salpingectomy, together with appendectomy, was performed in 1939; pregnancy and cesarean

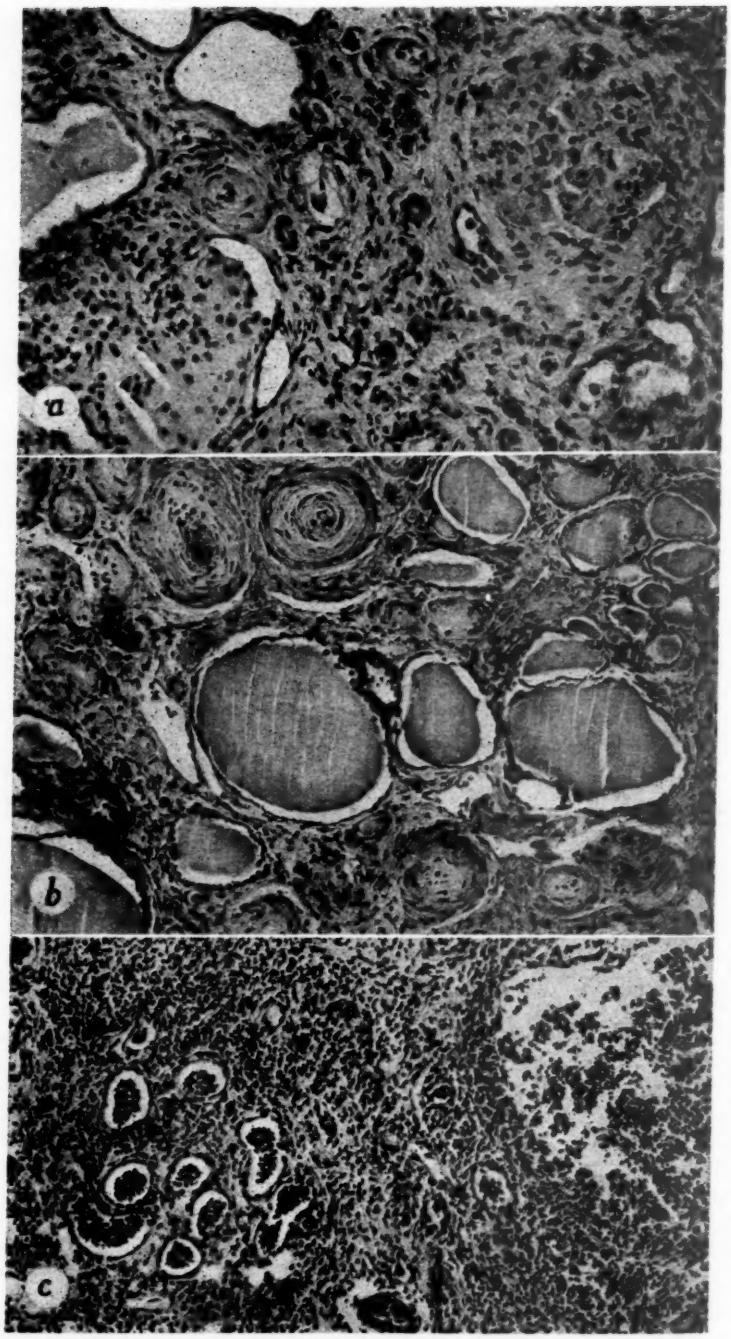

Fig. 10.—(Case 2.) *a*, Glomeruli are destroyed and replaced by hyalinized connective tissue (hematoxylin and eosin, ×150). *b*, Dilated tubules filled with acidophilic material (so-called colloid casts). Marked thickening of walls of arteries and arterioles (hematoxylin and eosin, ×110). *c*, Purulent exudate in tubules and interstitial tissue. Small abscess may be noted to right (hematoxylin and eosin, ×90).

section for placenta previa in April, 1943. The present illness began in October, 1943, with the development of migratory arthritic pains in several joints. Anemia was noticed by her physician. Later there were mild swelling of the joints of both hands, wrists, and elbows and a rise in body temperature. In November, the fever recurred and edema of ankles and legs appeared and persisted. In January, 1944, pitting edema became general and the patient's eyelids were affected. Afternoon fever up to 101° F. and sweating occurred. The urinary output diminished at this time and her physician found on urinalysis albuminuria and pyuria. The extent of edema fluctuated during February, but during the week before coming to the clinic it increased distinctly and the patient gained seven pounds (3.2 kg.). During that week the patient noticed pain in the left anterior part of the thorax and dyspnea on exertion. In the two to three months before admission she had on several occasions passed watery stools.

On physical examination the patient was 66½ inches (168.9 cm.) tall and weighed 120 pounds (54.4 kg.). She appeared to be slightly anemic. General edema, Grade 2, was present. The wrist and the joints of the right hand were swollen. The blood pressure was 125/75. Ophthalmoscopic examination revealed normal ocular fundi. Routine urinalyses revealed albumin, Grade 2 to 4, and no reducing substances. The sediment contained erythrocytes, Grade 0 to 2, and leucocytes, Grade 0 to 3. Quantitative estimation of urinary protein showed the presence of 0.2 to 0.8 Gm. in 100 cubic centimeters. In a single culture of urine, colon bacilli were present. Renal function was adequate as indicated by a standard urea clearance of 38 c.c., by a concentration of urea in 100 c.c. of blood of 28 mg., and by a urogram which revealed an early and considerable concentration of iodine compound in the renal calices and pelves. Blood studies indicated that results of the Kline flocculation test for syphilis were negative and secondary anemia was present. The hemoglobin concentration was 10.2 Gm. in 100 c.c., and the erythrocytes numbered 3,200,000 per cubic millimeter. The content of protein and albumin in the serum were definitely decreased and the lipoid concentration in the plasma increased (Table IV). The electrocardiogram taken on February 28 was considered to be essentially normal (Fig. 11). A provisional diagnosis of subacute glomerulonephritis with nephrotic features was made. The history and some minor alterations in the calices of both kidneys as seen in urograms suggested mild chronic bilateral pyelonephritis.

The course of the patient's illness while she was in the hospital, from February 23 to March 21, was quite satisfactory. The edema responded to certain diuretic procedures, including diet, potassium nitrate, and three transfusions of blood (1,500 c.c. in all). The daily volume of urine varied from 700 to 2,400 cubic centimeters. The patient lost 18 pounds (8.2 kg.), and edema disappeared. The hemoglobin in the blood rose to normal and there was an increase in the serum protein and albumin. Arthritic manifestations were minimal, and her temperature was usually about normal though on a single occasion it rose to 100.6° F. A satisfactory explanation of the rheumatic complaints and manifestations of arthritis which she had on admission could not be made. On March 20 the urea clearance was 37 cubic centimeters.

After returning home on March 21 the patient felt much stronger and in the next three weeks gradually resumed her household duties. However, on April 6 the temperature rose to 102.5° F. and the following day the joints of her fingers and wrist began to swell. Later the periodic diarrhea and pain in the left anterior portion of the thorax recurred.

The second admission was on April 18, 1944. On examination the patient's temperature was 102° F., there was a butterfly papuloerythematous rash on her face, and the joints of her fingers were swollen. The heart rate was 100 beats per minute and no murmurs or rubs were heard. Edema, Grade 2, was present in the legs. The blood pressure was 115/70 and on ophthalmoscopic examination the fundi were essentially normal, although the retinal arterioles and veins seemed distinctly dilated. A roentgenogram of the thorax revealed a possible mitral configuration of the heart. Several routine urinalyses revealed findings similar to those on her first admission; the quantitative estimate of protein in the urine was 0.1 to 0.5 Gm. in 100 cubic centimeters. Constituents of the blood were: hemoglobin, 10 Gm.; erythro-

TABLE IV. DATA ON BLOOD IN CASE 3

DATE (1944)	WHOLE BLOOD: HEMOGLOBIN (GM. IN 100 C.C.)	WHOLE BLOOD: UREA (MG. IN 100 C.C.)	WHOLE BLOOD: CREATININE (MG. IN 100 C.C.)	BLOOD SERUM: NON-PROTEIN NITROGEN (MG. IN 100 C.C.)	BLOOD SERUM: PROTEIN (GM. IN 100 C.C.)	BLOOD SERUM: ALBUMIN (GM. IN 100 C.C.)	BLOOD SERUM: ALBUMIN-GLOBULIN RATIO	BLOOD SERUM: POTASSIUM (MG. IN 100 C.C.)	BLOOD SERUM: SULFATE (MG. IN 100 C.C.)	BLOOD PLASMA: CHLORIDE (MG. IN 100 C.C.)	BLOOD PLASMA: CARBON DIOXIDE COMBINING POWER (VOLUMES IN 100 C.C.)	ELECTROCARDIOGRAM
2/23	10.2	28										
2/24				28	4.6							
2/25*		20										
2/28				34	3.9	2.0	1.1/1.0	15.6	5.2	660	50	ECG
3/1†												
3/ 9		96	1.2	89	5.7	2.8	1.0/1.2	20.9	12.3			
3/15‡		60	1.2					21.4	7.9			
3/18	13.3											
3/20		42							7.1			
4/18§	10.0	56		55	4.2	2.0	1.0/1.1		10.8			ECG 4-19
4/20‖								23.3		574		ECG 4-20, 21
4/22¶												ECG
4/28		90	1.5									ECG 4-24, 26
5/ 5		144	2.5	105	3.3	1.4	1.0/1.3					ECG 4-29, 5-1
5/ 6		130						22.2	11.4	583		ECG
5/15		164	2.1									
5/22		Patient died										

*Plasma cholesterol, 327 mg. in 100 cubic centimeters.

†Serum calcium, 7.9 mg.; serum phosphorus, 4.1 mg. in 100 cubic centimeters.

‡Plasma cholesterol, 240 mg.; cholesterol esters, 203 mg.; lecithin, 405 mg.; total fatty acid, 747 mg.; total lipoids, 987 mg. in 100 cubic centimeters.

§Plasma cholesterol, 277 mg., total fatty acid, 546 mg.; total lipoids, 823 mg. in 100 cubic centimeters.

‖Plasma cholesterol, 293 mg.; cholesterol esters, 182 mg.; lecithin, 458 mg.; total fatty acid, 712 mg.; total lipoids, 1,005 mg. in 100 cubic centimeters.

¶Vitamin C content of plasma, 0.5 mg. in 100 cubic centimeters.

cytes, 3,740,000; leucocytes, 5,200 to 13,400; urea, 56 mg.; serum sulfate, 10.8 mg.; serum protein, 4.2 Gm.; and the total lipoids of the plasma from 823 to 1,005 milligrams. The results of the Kline, Kahn, Hinton, and Kolmer tests of the blood serum for syphilis were negative.

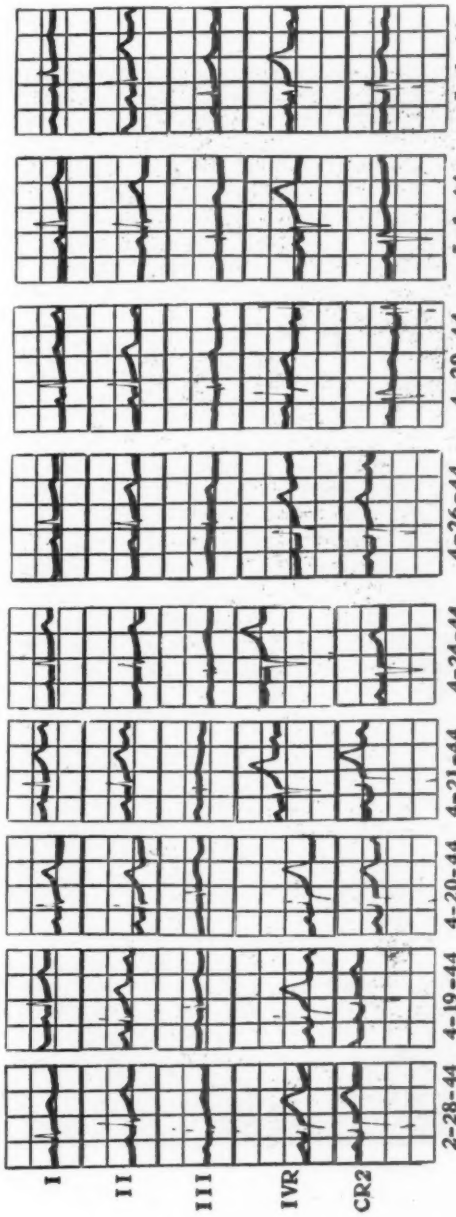

Fig. 11.—(Case 3.) Only by comparison of serial tracings is it possible to define changes suggestive of pericarditis. High-peaked T waves in Lead I are present in tracings taken on April 20 and 21 when a pericardial friction rub was first audible. The appearance of slight elevation of the RS-T segment in Lead III in the electrocardiogram of April 29 coincided closely with reappearance of the friction rub.

The patient was evidently still suffering from chronic glomerulonephritis in a nephrotic phase, but, in addition, evidences of toxemia including fever and an erythematous lesion in the skin of the face had developed.

On April 19 a soft systolic murmur could be heard over the mitral region of the heart. The patient complained of pain in the left side of the thorax and dyspnea. During the afternoon of April 20 her temperature rose to 102.6° F., and a definite precordial friction rub developed and persisted for forty-eight hours. Electrocardiograms taken on April 19, April 20, and April 21 were not strikingly different from the initial electrocardiogram recorded two months earlier, on February 28. There was an increase in the height of the T wave in Leads I,

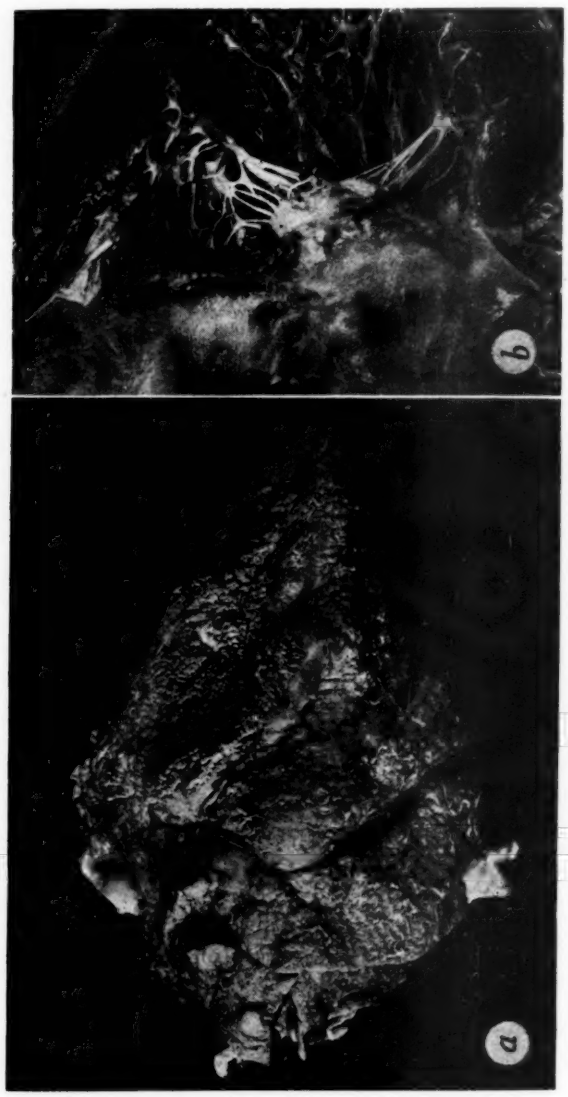

Fig. 12.—(Case 3.) *a*, Fibrinous pericarditis. *b*, Vegetative mitral endocarditis (nonbacterial).

II, and IVR and the apex of the deflection was sharper (Fig. 11). From April 23 to 27, inclusive, no friction rub was heard and the temperature did not rise above 99° F. In the electrocardiogram recorded on April 26, a slight change or elevation in the configuration of the RS-T segment in Lead III could be defined (Fig. 11). On April 28 and 29, a loud friction rub was audible. On April 29 the patient's temperature rose to 101.7° F. In the

electrocardiogram taken on this day the elevation of the RS-T in Lead III was somewhat more definite than that in the tracing made on April 26 (Fig. 11). During the remaining twenty-three days of the life of the patient a friction rub was heard over the heart intermittently. In the final tracing taken on May 6 (Fig. 11), no definite signs indicative of pericarditis were present.

On April 24 to 26 a loud blowing systolic murmur was heard over the apical region of the heart. Three attempts to grow an organism from the blood were unsuccessful. Uremia gradually developed, and on May 5 the concentration of urea in the blood had increased to 144 milligrams. The blood creatinine was elevated to 2.5 mg. on the same day, and on May 6 the serum sulfate increased to 11.4 milligrams. Because the patient had intermittent attacks of diarrhea, a roentgenogram of the colon was taken following a barium enema on May 9. Ulcerative colitis was found. Stomatitis was demonstrable on May 14 and signs of pneumonia were present in the lower lobe of the left lung the next morning. Up to this time the daily volume of urine during this stay in the hospital varied from 800 to 1,500 cubic centimeters. From May 14 until her death, eight days later, the patient lapsed periodically into semicoma, found it difficult to swallow food or fluids, and passed urine involuntarily. She died at 6:40 A.M., May 22.

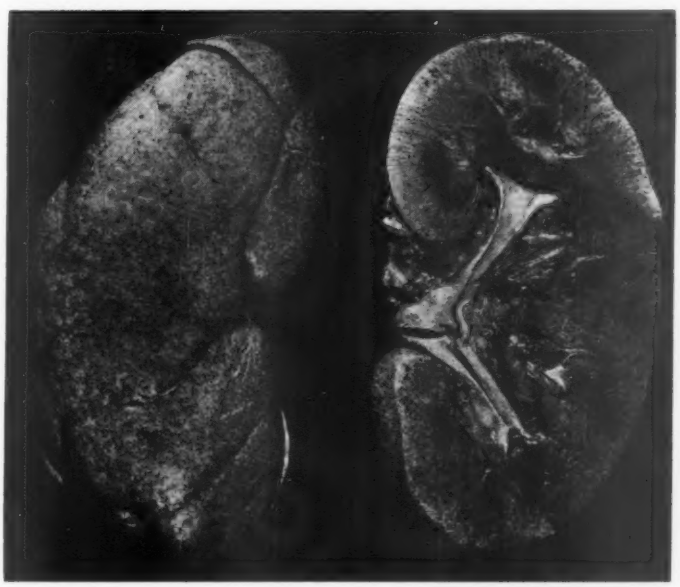

Fig. 13.—(Case 3.) Subacute glomerulonephritis.

Differences of opinion were often expressed as to the clinical diagnosis of this patient's condition while she was under observation in the hospital. However, shortly before her death we were convinced that she was suffering from a general diffuse disease and that the skin lesion, colitis, diffuse nephritis, endocarditis and pericarditis were manifestations of the disorder which Libman and Sacks[10] first described in 1923 and since has been termed by many as the "Libman-Sacks syndrome."[11]

Necropsy.—There was moderate pretibial edema. The peritoneal cavity contained 500 c.c. of cloudy, opalescent fluid. There were fibrinous adhesions from the omentum to the bladder, descending colon, uterus, and anteriorly to the abdominal wall. The right pleural cavity contained 750 c.c. of fluid and flecks of fibrin. There were fibrinous adhesions between the pericardium and lung. The left pleural cavity contained 1,500 c.c. of dark amber fluid. The pericardial sac measured 16 cm. in transverse diameter and contained 250 c.c. of sanguino-

fibrinous exudate. Fibrinous exudate covered the visceral and parietal layers of the pericardium (Fig. 12, *a*).

The heart weighed 336 grams (normal, 230 grams). The mitral valve was thickened and edematous. There was a row of granular, pyramidal-shaped vegetations along the line of closure of most of the posterior mitral leaflet and a similar but shorter row on the

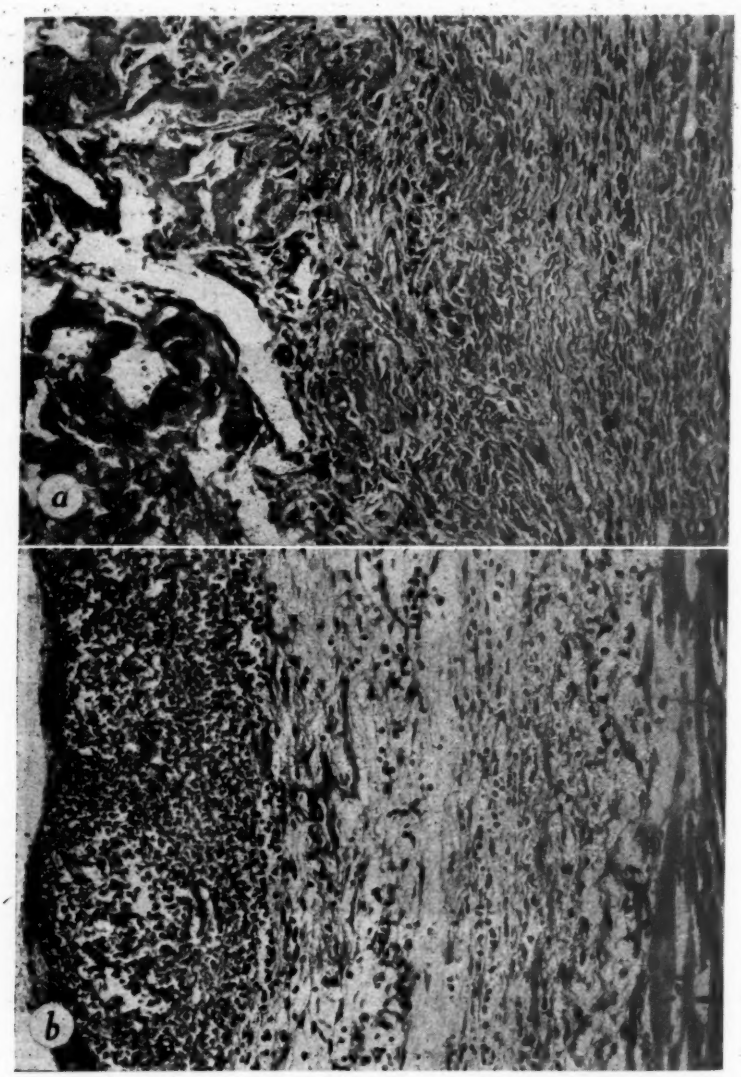

Fig. 14.—(Case 3.) *a*, Pericarditis. Organization of the fibrinous exudate by fibroblasts can be seen (hematoxylin and eosin, ×130). *b*, Mural endocarditis. Edema and fibrinopurulent exudate are shown (hematoxylin and eosin, ×135).

anterior leaflet (Fig. 12, *b*). Some of these vegetations extended over the surface of the leaflet and up on the auricular wall. Similar granular but flatter vegetations were also found on the chordae tendineae. On the endocardial surface of the left ventricle, 2 cm. below the aortic valve, there was a flat granular mural vegetation. There were a few small vegetations on both surfaces on the tricuspid leaflet.

The pleura of the lungs contained many petechiae. There was granular fibrinous exudate on the pleural surface of the right lower lobe. Firm, nodular consolidated areas could be felt in both lower lobes. The left lung was almost completely collapsed.

The right kidney weighed 170 grams and the left weighed 194 grams. Aside from a slightly granular surface and a few small petechiae, the kidneys were not remarkable grossly (Fig. 13). The brain appeared grossly normal except for a few small petechiae in the left basal nuclei.

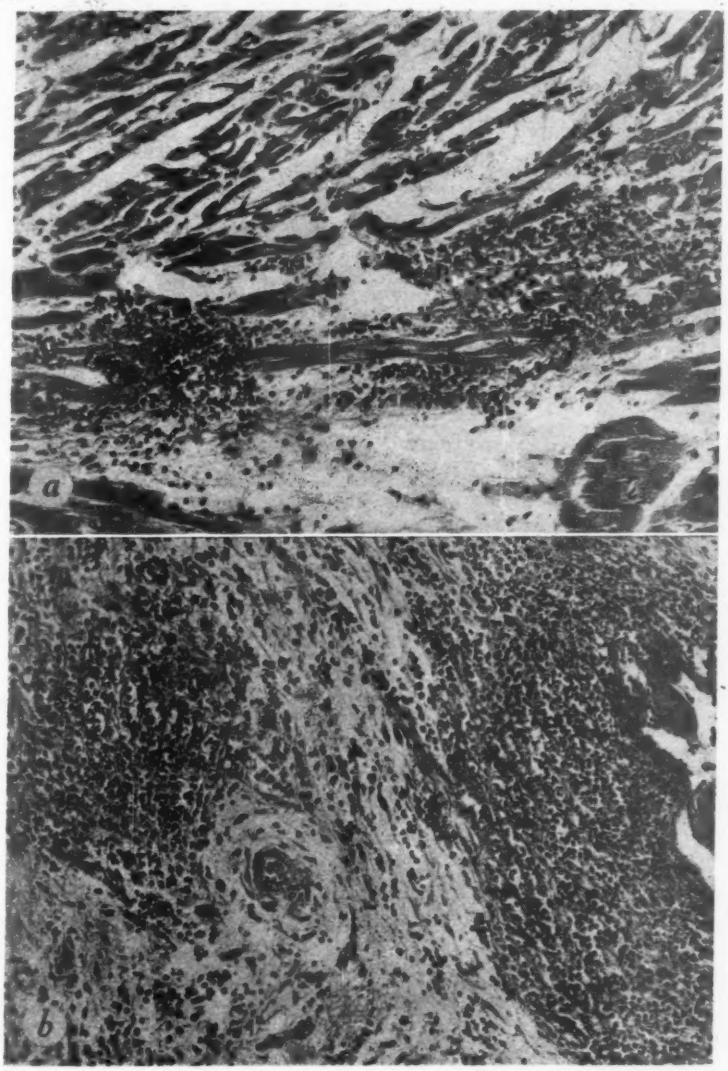

Fig. 15.—(Case 3.) *a*, Myocarditis. Focal collection of polymorphonuclear cells and necrosis of muscle fibers can be noted (hematoxylin and eosin, ×145). *b*, Mitral endocarditis. Fibrinoid degeneration of connective tissue, necrosis, and purulent exudate (hematoxylin and eosin, ×135).

Histologic Examination.—There was a thick fibrinous exudate over the pericardial surfaces. Organization of this exudate by masses of fibroblasts was taking place (Fig. 14, *a*). Although most of the fibrinous exudate was acidophilic, there were many masses and threads of fibrin which took the hematoxylin stain. Sections of the left ventricle and auricle revealed

a fibrinopurulent exudate on the endocardial surface (Fig. 14, *b*). In the myocardium there were hyaline thrombi in small vessels and focal and interstitial collections of polymorphonuclear cells with necrosis of some muscle fibers (Fig. 15, *a*). In sections of the mitral valve the vegetations were found to consist largely of fibrinopurulent exudate (Fig. 15, *b*).

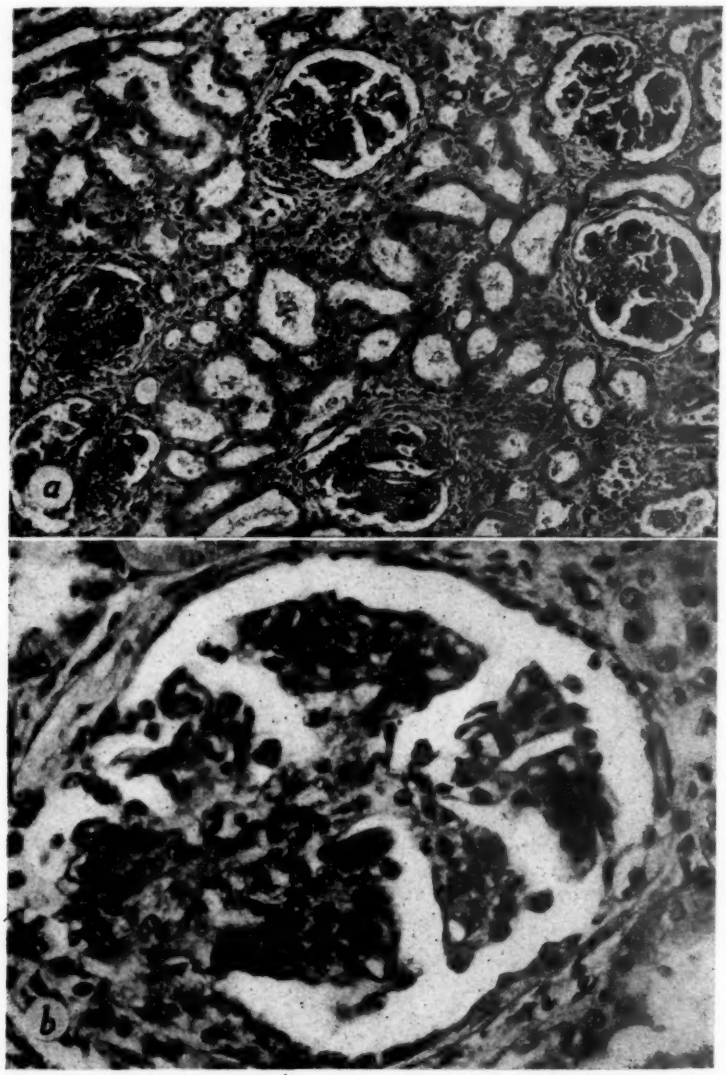

Fig. 16.—(Case 3.) *a* and *b*, Subacute glomerulonephritis. Proliferation of endothelial cells, fusion, and focal necrosis (*a*, hematoxylin and eosin, ×90; *b*, ×325).

There were patches of fibrinoid degeneration of the connective tissue of the leaflet with actual necrosis in some places. Large numbers of polymorphonuclear cells were present in these areas. In addition to these foci there was an acute diffuse inflammation of the entire leaflet. The latter was well vascularized by capillaries as well as by arteries and veins. The tricuspid valve was the seat of a similar but less extensive inflammatory process.

In sections of the kidney no normal glomeruli could be found. The most pronounced change was an extensive increase in the number of endothelial cells in the capillaries. This

had produced very cellular glomerular tufts and occlusion of the capillaries. Fusion and necrosis of these endothelial cells and various portions of the tufts had occurred. Adhesions of the tuft to the capsule were observed frequently. Hyaline thickening of the basement membrane of the capillaries (wire looping) and fibrous crescents were occasionally found. The tubules generally appeared normal. Frozen sections stained for fat revealed a mild degree of infiltration of fat into some of the epithelial cells of the convoluted tubules. A few tubules contained red blood cells and a few contained albuminous material. The arteries and veins appeared normal (Fig. 16, *a* and *b*).

Section of the lung revealed a fibrinopurulent pleuritis, purulent bronchitis, and lobular pneumonia. In sections of the right main stem bronchus there was a bandlike area of fibrinoid degeneration and necrosis immediately beneath the epithelium.

There was severe edema of the submucosa of the colon.

The following diagnoses were made: (1) vegetative mitral, tricuspid, and mural endocarditis; (2) fibrinous pericarditis, pleuritis, and peritonitis; (3) subacute glomerulonephritis; (4) bronchopneumonia; (5) focal myocarditis; (6) edema of mucosa of colon; (7) hypertrophy of heart; and (8) petechiae of left basal nuclei of brain.

OBSERVATIONS

Clinical Observations.—It was possible in three cases, by clinical observation, to recognize the early development of acute pericarditis and follow its subsequent course. The initial rub over the precordium was first audible thirty days, seven days, and thirty-three days before death in Cases 1, 2, and 3, respectively. This period of one to four and one-half weeks provided an unusual opportunity to study pericarditis during its entire course. Observations, including electrocardiograms, which could be used as controls were made in two cases during a previous visit of the patients to the clinic and in all three cases at the time of last admission to the hospital. In Case 2, in which the patient made only one visit to the clinic, clinical, chemical, and electrocardiographic observations extended over a period of forty days before the onset of pericarditis.

Cases 1 and 2 presented the clinical features so often seen in terminal chronic uremia. Perhaps the most striking objective development in these two cases was that of a diffuse membranous stomatitis, so-called uremic frost. It occurred in each instance at approximately the time of onset of the pericarditis. The toxemia due to uremia was severe, as indicated by convulsive seizures and mental disturbances. A noticeable increase in temperature occurred with the onset of pericarditis. It is of some interest that in Case 1 after the initial development of pericarditis there followed an interim period of fourteen days during which the temperature fell to the normal level and the pericardial rub was no longer audible. Subsequently, a rise in temperature accompanied the recurrence of the rub. In contrast, in Case 2 the signs of pericarditis persisted from onset throughout the course. In the experience of most observers this is the usual course of events in similar cases. In Case 3 the primary cause of renal, pericardial, and other pathologic lesions is the little-understood etiological factor in the Libman-Sacks syndrome.[10, 11] Therefore, toxemia of uremia was probably a secondary and minor causative factor.[12] In this case the pericardial rub and increase of body temperature occurred almost simultaneously. These

were intermittent as in Case 1. The increase in temperature, however, was more definite than in Cases 1 and 2. The course of the pericarditis in Case 3 was the longest. The development of stomatitis and mild colitis during the course of the pericarditis is of interest.

Chemical Studies of Blood and Urine.—The greatest alterations in the blood and urine occurred in Case 1. The concentrations of urea, creatinine, sulfate, and phosphorus in the blood were extremely high throughout the last illness (Table I). The lipoid content of the plasma was also increased. The concentration of potassium in the serum varied from an abnormally low content to a slight increase above the normal. The decrease in concentration of hemoglobin, chloride, sodium, and calcium in whole blood, plasma, and serum was also typical of severe uremia. Hypoproteinemia was moderate in degree and there was slight, if any, tendency to acidosis, the carbon dioxide combining power varying from 62 to 38 volumes in 100 cubic centimeters. The balance of total basic to acid ions is distinctly on the basic side (Table II). The excretion of protein in the urine was considerable, amounting to about 1 to 2 Gm. in 100 cubic centimeters.

In Case 2 also the chemical evidence of uremia was definite. However, the urea, creatinine, sulfate, and phosphorus indicated less renal insufficiency than in same period of illness in Case 1. The rise in potassium was somewhat greater than in Case 1. There was only a slight increase in plasma lipoids. The hypoproteinemia was moderate in degree. In addition to the anticipated decrease in concentration of hemoglobin, chlorides, and sodium, definite acidosis was present as demonstrated by the carbon dioxide combining power of the plasma of 24 volumes in 100 c.c. on the day of death. This finding differs from that in Case 1 in which there was little or no acidosis. The protein content of the urine (0.3 Gm. in 100 c.c.) was also distinctly less than in Case 1.

The alterations in the blood in Case 3 reveal a distinctly milder degree of uremia than in the other two cases.[12] Urea, creatinine, and sulfate rose only to 164, 2.5, and 11.4 mg., respectively. The potassium concentration fluctuated at the upper limit of normal. There was a definite increase, greater than in Cases 1 and 2, in all the lipoid fractions of the plasma. The reduction in the content of serum protein and albumin was considerable. These alterations in protein and lipoid content were in harmony with the distinct tendency to nephrosis in this patient. The terminal reduction in the hemoglobin in Case 3 was distinctly less than in the other two cases. This finding, together with the observation that the hemoglobin increased rapidly after transfusions during the patient's first visit, indicates a much less toxic condition of the bone marrow than is usually the case in chronic, severe uremia (Cases 1 and 2). The concentration of protein in the urine at the time of the patient's first admission was considerable, varying from 0.2 to 0.8 Gm. in 100 cubic centimeters. There was additional evidence as late as one month before the onset of pericarditis that renal function was not as severely impaired as in Cases 1 and 2, for at that time the standard urea clearance was 37 c.c., an approximately normal value.

Electrocardiographic Observations.—The degree of RS-T segment elevation and the changes in T-wave configuration in the electrocardiograms reproduced

are not exceptionally great. However, in Cases 1 and 2, the changes were of sufficient extent to be definitive,[13] and in all three cases, such alterations as did occur were coincidental with the other manifestations of the pericarditis. In Case 2, slight changes appeared in the electrocardiogram five days before a friction rub was audible. In Case 1 no definite electrocardiographic changes were recorded until five days after a friction rub was first heard. In general, however, the period of maximal intensity of the friction rub coincided with the occurrence of maximal electrocardiographic changes of the type associated with pericarditis. It is of interest that in Cases 1 and 3 both the friction rub and the electrocardiographic changes disappeared only to reappear at a later time (Table V).

TABLE V. RELATION OF AUDIBLE PERICARDIAL RUB AND BODY TEMPERATURE TO ELECTROCARDIOGRAPHIC DATA

CASE	DATE	PERICARDIAL RUB*	BODY TEMPERATURE, DAILY MAXIMUM (°F.)	ELECTROCARDIOGRAM†	
				RS-T SEGMENT ALTERATIONS	T-WAVE ALTERATIONS
	1943				
1	6/11	Inaudible	99	0	0
	6/16	Distinct‡	98.6		
	6/17	Inaudible	100	0	0
	6/21	Loud	100.2	+	+
	6/23	Loud	99.4	+	+
	6/24	Loud (4)	99.4		
	6/25	Inaudible	98.6	+	+
	6/28	Inaudible	98.6	±	±
	7/ 2	Inaudible	98.6	±	±
	7/ 7	Inaudible (13)	100		
	7/ 8	Loud	99	+	+
	7/14	Loud (7)	100.2	+	+
	1944				
2	2/11	Inaudible	97.4	0	0
	2/16	Inaudible	99.4	+	+
	2/20	Inaudible (10)	100.6		
	2/21	Loud	100.6	+	+
	2/23	Loud	100	+	+
	2/25	Loud	99	+	+
	2/26	Loud	98.4	+	+
	2/27	Loud (7)	98		
3	2/28	Inaudible	97	0	0
	4/19	Inaudible	103.4	0	+
	4/20	Loud	102.6	0	+
	4/21	Loud	99.4	0	+
	4/22	Loud (3)	98.7		
	4/24	Inaudible	98.6	0	+
	4/26	Inaudible	98.6	+	+
	4/27	Inaudible (5)	99		
	4/28	Loud	99.6		
	4/29	Loud (2)	101.7	+	
	5/ 1	Inaudible	98.8		
	5/ 3	Inaudible (3)	100.4		
	5/ 6	Loud (3)	102	0	0
	5/ 8	Inaudible (2)	100.4		

*The numbers in parentheses indicate the number of consecutive days in which the condition was present.

†0 = No distinctive alterations. + = Elevation of RS-T segment or T wave. ± = Isoelectric RS-T segment or isoelectric or diphasic T wave.

‡Distinct but not loud rub.

Pathologic Observations.—The gross appearance of the pericardial inflammation varied greatly.[14, 15] In Case 1 the exudate was predominantly hemorrhagic; in Case 2 it was purulent; and in the third case it was fibrinous. The histologic study of the inflammatory process did not answer the question of what etiological factors were concerned. The exudate in Case 1 was more hemorrhagic than is usually observed in so-called uremic or "chemical" pericarditis, but no apparent reason for this could be demonstrated histologically. In Case 2 the purulent character of the exudate coincided with the finding of colonies of bacteria which were gram-positive cocci. The exact nature of the organisms could not be determined because cultures were not obtained. The possibility that they were post-mortem invaders must be considered. No organisms could be demonstrated in Case 3. In all three cases the well-developed organization of the pericardial exudate indicated that the inflammatory process had been present for some time. In Case 1, in addition to the exudative lesion, there were organizing fibrinous adhesions which suggested a healing process. These findings support the clinical observations of initial pericarditis, remission, and later recurrence. Myocardial lesions were found only in Case 3.

The renal lesions deserve comment. In Case 1 there was typical glomerulonephritis. The fact that lesions identical with those described as Kimmelstiel-Wilson's disease[9] were also present emphasizes the nonspecific character of so-called intercapillary glomerulosclerosis. Identical lesions have also been observed by others in cases of hypertension and cases of glomerulonephritis without diabetes.[16] The fact that no normal glomeruli could be found gives histologic support to the clinical diagnosis of renal insufficiency. The renal lesions in Case 2 were largely those of active and healed pyelonephritis. The possibility that chronic glomerulonephritis also was present cannot be entirely dismissed since few normal glomeruli could be found. Nevertheless, it is well known that glomerular destruction also occurs extensively in pyelonephritis. The renal lesions in Case 3 represented a more recent inflammatory process than was present in Cases 1 and 2. The lesions were much more extensive than those usually observed in lupus erythematosus or Libman-Sacks disease. The diffuse proliferation of the endothelium of the glomerular capillaries, the focal necrosis of portions of the glomerular tuft, and the occasional occurrence of hyaline thrombi in the glomerular capillaries and afferent arterioles resembled strongly the type of lesion found in subacute bacterial endocarditis. Nevertheless, similar lesions have been observed in cases of lupus erythematosus in the absence of endocarditis[17] and in uncomplicated glomerulonephritis. The histologic features of the cardiac lesions of this case and the persistently negative blood cultures were consistent with a diagnosis of lupus erythematosus or Libman-Sacks disease.

COMMENT

The occurrence of pericarditis in chronic uremia has in the past been considered a final incident in the course of the disease.[18] There is evidence, however, that, even in the late stages of chronic uremia, pericarditis may develop and run its course and healing may take place. Such cases have been reported

by Chauffard and Huber,[19] Marantis,[20] Leplat,[21] and Barach.[22] The present study goes further in revealing both clinical and electrocardiographic evidence that pericarditis can occur, subside, and recur in the same uremic patient. The pathologic lesions found at necropsy in Case 1, after pericarditis had been present intermittently for one month, were compatible with an intermittent course.

The comparatively slight changes in the electrocardiogram throughout the course of the pericarditis in Case 3 indicate that persistent fibrinous pericarditis of considerable degree can take place with minimal electrocardiographic alterations. This suggests the possibility that demonstrable electrocardiographic changes may be entirely absent in acute pericarditis. Such a suggestion is consistent with the observations of previous investigators.[23] This study of three cases emphasizes that during the course of uremic pericarditis only minimal disturbances may occur in the distribution of the electrical potentials developed in the heart.

The variability among cases in the degree of electrocardiographic changes occurring during episodes of pericarditis is not readily explained. Since only small amounts of fluid were found in the pericardial sac in all three cases, the presence or absence of electrocardiographic changes can not be ascribed to cardiac tamponade, nor is the variability in electrocardiographic changes to be accounted for solely on the basis of existence of myocarditis.[23] In only one of the three cases (Case 3) was there histologic evidence of myocarditis, and it was in this case that electrocardiographic indications of pericarditis were appreciable only on closest scrutiny of serial tracings. Electrocardiograms were taken at relatively short intervals before, during, and after the friction rub could be heard. When electrocardiographic alterations occurred, they evolved slowly. Hence, it is unlikely that significant changes in the distribution of electrical potentials existed for some brief interval but were not recorded.

Just why in some cases the potentials which develop after cellular injury are productive of significant electrocardiographic changes, whereas in other cases they are not, remains an unanswered question. Perhaps, the solution should be sought in a study of the speed with which the pericarditis and the attendant cellular injury progress and regress. But that a complete answer would be obtained by such a study appears doubtful.

The actual cause of pericarditis in uremia is not understood. Several possible factors can be eliminated in our cases. Syphilis and tuberculosis were absent. There were no evidences of septicemia in Cases 1 and 3. The pathologic and bacteriologic studies of Barach[22] show that uremic pericarditis may have an infectious origin in some cases while in others no bacteria or tissue reactions of infection are present. The histologic lesion in Case 2 is suggestive of an infectious process, but similar changes were absent in Cases 1 and 3. What then can be the toxic etiological factor? This question was raised by Duhot and Hallez in 1913.[24] The presence of a definite acidosis in the blood in certain of his cases led Barach to consider acidosis as a possible toxic factor. But the findings of several subsequent investigators indicate that grave uremia can be

present in the absence of severe acidosis.[25] This fact receives added confirmation in the data recorded in Case 1. Other significant alterations of the inorganic ions in the blood occur in uremia. These include a decrease in concentration of chloride, sodium, and calcium and increase in the concentration of phosphate, sulfate, and potassium. In our cases none of these changes, single or combined, appear to have definite significance as a cause of the pericarditis. The actual concentration of serum potassium in this series is interesting. Only in Case 2 did the serum potassium increase appreciably. The highest level was 25.6 mg. in 100 c.c., and this concentration does not usually lead to alterations in electrocardiographic tracings such as occur in pericarditis. It is interesting that when both potassium intoxication (serum potassium, 40 mg. in 100 c.c.) and pericarditis occurred in one of our patients in a former series of cases of uremia, the electrocardiogram revealed intraventricular block, but no RS-T segment changes typical of pericarditis.[26] Therefore, the concentration of potassium ions in the serum is not a decisive factor in the development of the electrocardiographic changes characteristic of pericarditis.

New microchemical methods have greatly increased knowledge of the many chemical alterations that can occur in chronic uremia, but to date no alteration in a single chemical constituent, nor a combination of changes in the blood has been found which invariably accompanies the clinical picture of uremia including pericarditis. All the known data support the conception of chemical uremia in which infection may play a secondary role.

CONCLUSIONS

Acute pericarditis occurs frequently in chronic uremia. Clinical, electrocardiographic, and pathologic studies indicate that uremic pericarditis is a process which undergoes exacerbations and remissions and may even heal. It is an incident in the course of advanced renal insufficiency, but not inevitably a terminal incident. Like so many of the complications of uremia, its actual etiology is still unknown. However, the greatly altered chemistry present in the uremic patient must be an important etiological factor.

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PAROXYSMAL VENTRICULAR TACHYCARDIA

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CLINICAL experience has led us to regard paroxysmal ventricular tachycardia as a very serious condition. This arrhythmia is usually associated with acute myocardial infarction or with digitalis intoxication and may be followed by ventricular fibrillation and death. However, a few instances of paroxysmal ventricular tachycardia have been reported in which there were no signs of organic heart disease.

The purpose of this communication is to report four unusual instances of ventricular tachycardia from which the patients recovered. In one instance, the tachycardia complicated myocardial infarction and persisted for twenty-six days. In another (Case 4), the electrocardiogram showed the rarely occurring condition of alternating direction of ventricular complexes during the paroxysmal tachycardia. In the other two (Cases 2 and 3), the attacks occurred in patients without organic heart disease.

CASE 1.—J. G., a 54-year-old farmer, gave a history of scarlet fever at the age of 14 years. There was no history of rheumatic fever. In January, 1941, he noticed a heavy pressure in the cardiac region, especially after meals. The pressure gradually became continuous, very severe, and was accompanied by pain radiating to both arms. He remained in bed for two months. He took 0.1 Gm. (1½ grains) of digitalis twice daily for eleven months. On Dec. 5, 1941, he suddenly felt a "flushing sensation" in the chest for which he was hospitalized. He had suffered no definite pain and only slight shortness of breath.

Examination revealed a strongly built man whose height was 5 feet 8 inches and whose weight was 178 pounds. There was slight pallor and slight engorgement of the cervical veins. The heart was not enlarged; the rhythm was regular, and the rate was 180 per minute. The sounds were of normal quality. The second aortic and pulmonic sounds were faint. The blood pressure was 90/70. The physical examination was otherwise negative.

The temperature, sedimentation rate, and white blood count were normal. The Kahn test was negative. Carotid sinus and ocular pressure had no influence on the cardiac rate. The electrocardiogram showed ventricular tachycardia (Fig. 1, *a*).

An intravenous injection of 10 c.c. of 25 per cent magnesium sulfate had no effect. Quinidine sulfate was then administered in doses of 6 grains every four hours, a total daily dose of 36 grains. Since this dosage proved ineffective, it was increased on the seventh day to 8 grains every four hours (total daily dose, 48 grains). This dosage also failed to control the attack (Fig. 1, *b*).

Digitalis was then given in doses of 3 grains twice daily, but was discontinued after three days because of nausea and vomiting. On the fifteenth day, quinine dihydrochloride in a dose of 7½ grains was given intramuscularly and 8 grains of quinidine sulfate were administered orally every four hours. Both drugs were well tolerated by the patient, but the attack remained uncontrolled. During the following days the intramuscular injection of quinine

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dihydrochloride (7½ grains) was continued, and the oral dose of quinidine sulfate was increased to 8 grains every three hours. On the twentieth day the dose of quinidine sulfate was increased to 15 grains every three hours, but the attack persisted.

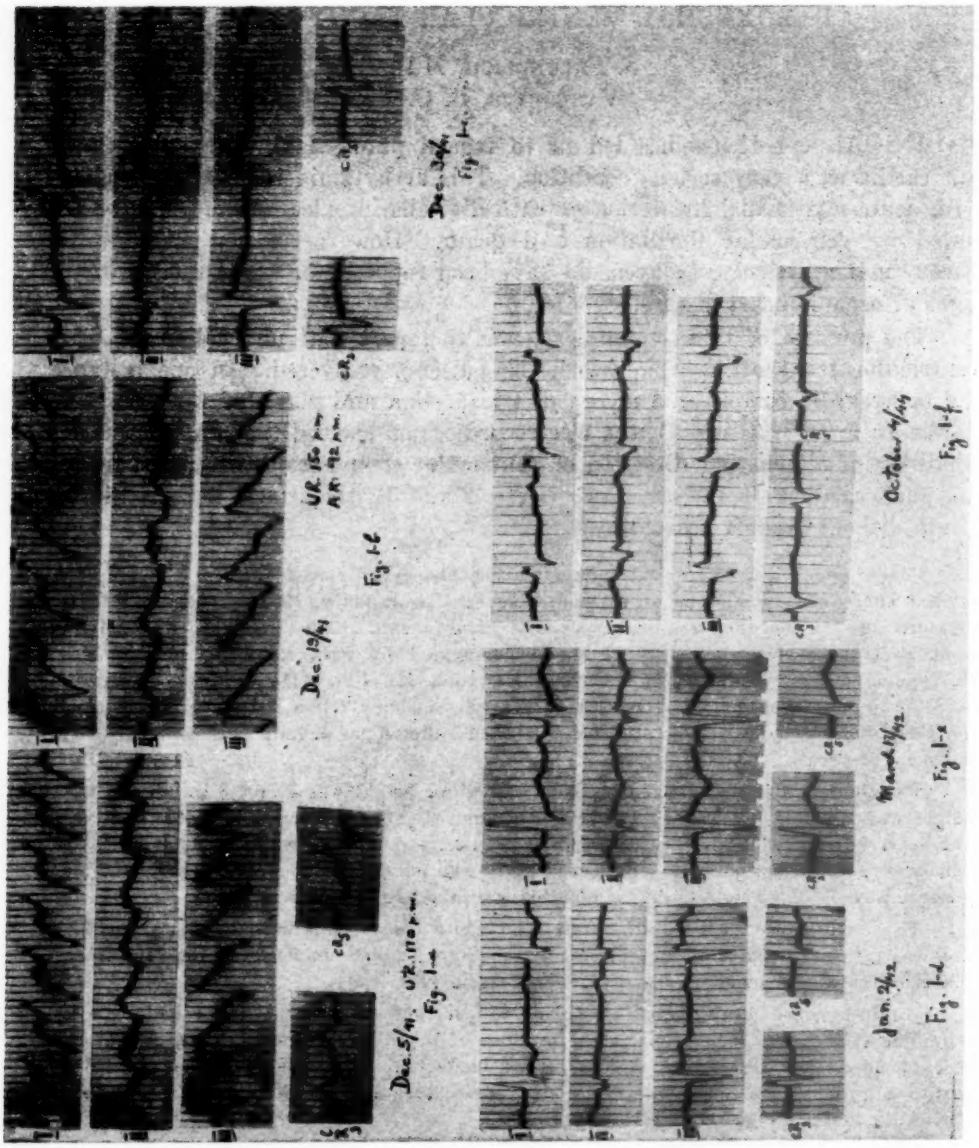

Fig. 1.

On the twenty-sixth day, in view of the continuous tachycardia, 30 grains of quinidine sulfate were given in a single dose at 10 A.M. Two hours later, since the rhythm was unaffected, another dose of 30 grains was given. One hour later the patient developed an ashen pallor, perspired profusely, became nauseated, and vomited a large amount of undigested food. At 5 P.M. a sudden change in rhythm occurred. The cardiac action became regular with a rate of 80 beats per minute. The blood pressure was 85/55. The electrocardiogram showed regular sinus rhythm, a normal P-R interval, notched and widened QRS complex

(0.14 second), a slightly depressed RS-T segment in Lead I, and elevated RS-T segments in Leads II and III (Fig. 1, *c*).

During the following three days the patient was given three grains of quinidine sulfate once daily. He felt well except for slight nausea and troublesome hiccups. The cardiac rate averaged 84 per minute. The blood pressure was 105/60. The temperature, sedimentation rate, and white blood count were normal. On the fourth day after the cessation of the attack the patient was seized at 8 A.M. with another attack of paroxysmal tachycardia. The electrocardiogram showed the same form of ventricular tachycardia as had been recorded previously.

The patient was immediately given 9 grains of quinidine sulfate orally. Two hours later he was given 12 grains orally. Since the tachycardia was unaffected, an oral dose of 12 grains was repeated two hours later and at the same time an intramuscular injection of 7½ grains of quinine dihydrochloride was given. The patient felt slightly nauseated; two hours after the last administration normal rhythm reappeared. The heart rate was 90 per minute, the blood pressure was 100/60, and the electrocardiogram was similar to that taken after the first attack.

On the following days the patient felt well. The blood pressure gradually rose to 125/90. The electrocardiogram remained unchanged, except for the T wave in Lead I, which became distinctly negative (Fig. 1, *d*). The patient received six grains of quinidine sulfate once daily until he was discharged sixteen days after the second attack.

Subsequent Course.—The tachycardia did not reappear. The electrocardiogram showed the pattern of posterior wall myocardial infarction (Fig. 1, *e*). The patient felt well during the following three years, until October, 1944, when he suffered an attack of myocardial infarction. The electrocardiogram showed small, notched QRS complexes in all three leads and a small R wave in the chest leads (Fig. 1, *f*). He responded well to treatment and has no discomfort at present.

CASE 2.—L. D., a 39-year-old laborer, gave a history of pneumonia in childhood, an appendectomy at the age of 23, and gonorrhea at the age of 29 years. There was no history of rheumatic fever. He smoked ten cigarettes daily and took no alcohol.

In 1937, when he was 35 years of age, he experienced a sudden attack of palpitation while working. The attack lasted a few minutes and disappeared suddenly. From that time on the attacks occurred almost every week and lasted for two or three days. After the attack subsided the patient felt well and was able to resume his work.

On May 15, 1941, the heart was normal in size, the rhythm was regular, and the rate was 240 per minute. The heart sounds were normal, and the blood pressure was 100/60. The remainder of the examination was negative. The sedimentation rate and white blood count were normal. The Kahn test was negative. The electrocardiogram showed ventricular tachycardia with a ventricular rate of 240 per minute (Fig. 2, *a*). The P waves were clearly visible. The auricular rate was 100 per minute. Carotid sinus and ocular pressure had no influence on the cardiac rate.

The patient was given 6 grains of quinidine sulfate every three hours; after the third dose the attack subsided. The electrocardiogram showed regular sinus rhythm, a normal P-R interval, and a normal QRS complex. The T waves were of low amplitude and slightly inverted in Lead I, and of increased amplitude in Leads II and III. In the chest leads the R wave was absent and the T wave was inverted (Fig. 2, *b*). Nine days later the standard leads were normal but the R wave was still small in the chest leads. After two more days the electrocardiogram was normal (Fig. 2, *c* and *d*).

A single dose of six grains of quinidine sulfate was given daily for the following two weeks. Since the patient remained free of attacks he was discharged from the hospital at the end of this period. When he was seen two months later he stated that he felt well and had gained weight, but that he experienced frequent short attacks of tachycardia if quinidine was discontinued. A single dose of less than 9 grains had no effect on these attacks.

CASE 3.—J. E. A., 38, a housewife, was first seen on Sept. 3, 1942. She gave no history of rheumatic fever or of infectious diseases. After the birth of her second child, in

1936, she experienced for the first time a short attack of palpitation which lasted a few minutes. In 1941 and during the following years the attacks of palpitation became more frequent. They were particularly troublesome during the week preceding her menses, when an attack would last almost an entire day. The patient described the attack as a sudden appearance of irregular beats which were followed sometimes by a rapid beating of the heart which provided a brief fainting spell.

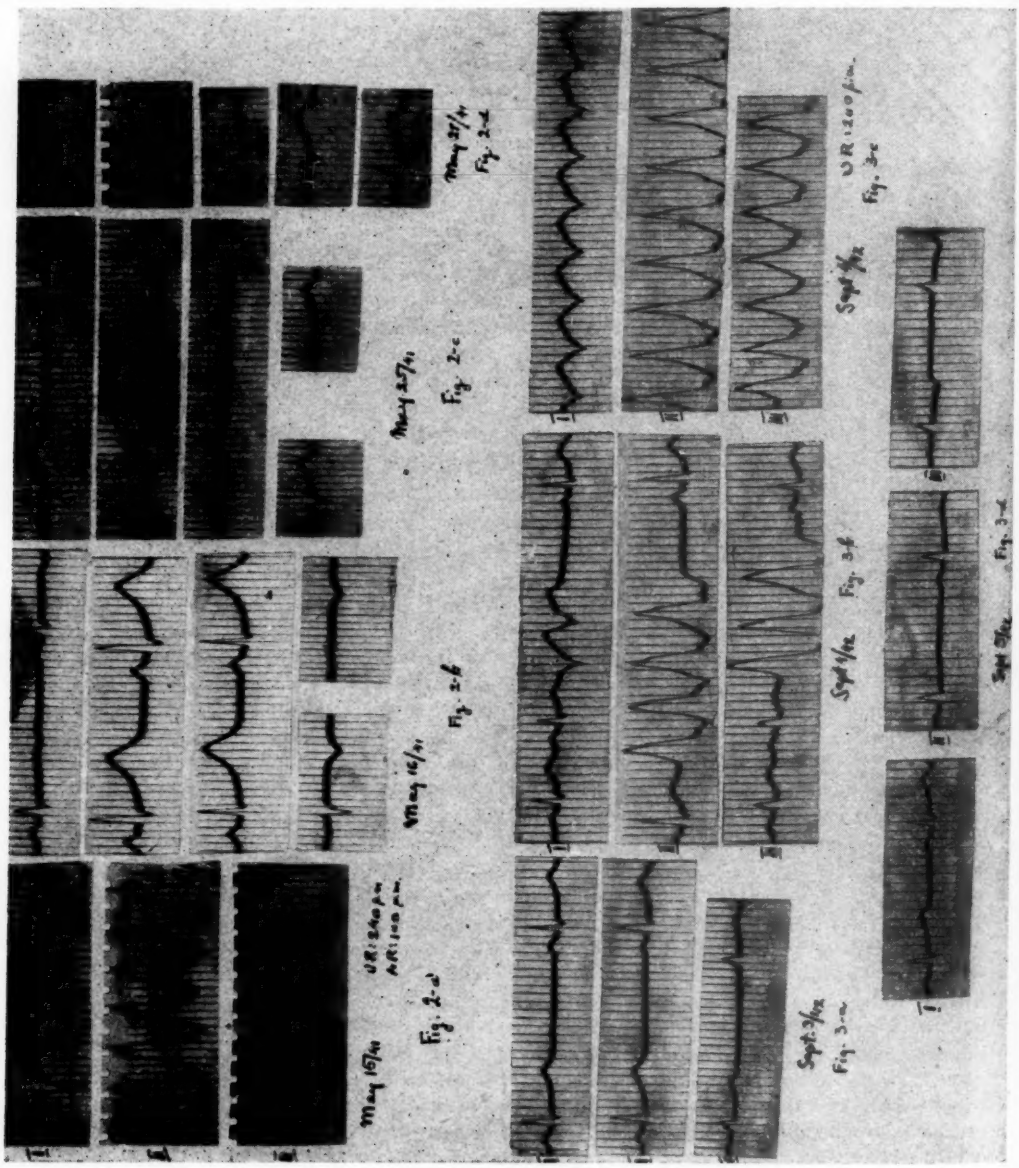

Fig. 2.

Physical examination disclosed a heart of normal size. No murmurs were audible. The rhythm was regular, and the rate was 64 per minute. The blood pressure was 120/65. Fluoroscopic examination revealed a heart normal in size and configuration. The temperature, white

blood count, and sedimentation rate were normal. The Kahn test was negative. The electrocardiogram was normal (Fig. 3, *a*).

On the following day, after a short walk, the patient noticed frequent irregular beats. An electrocardiogram showed coupled and quadrupled ventricular extrasystoles (Fig. 3, *b*).

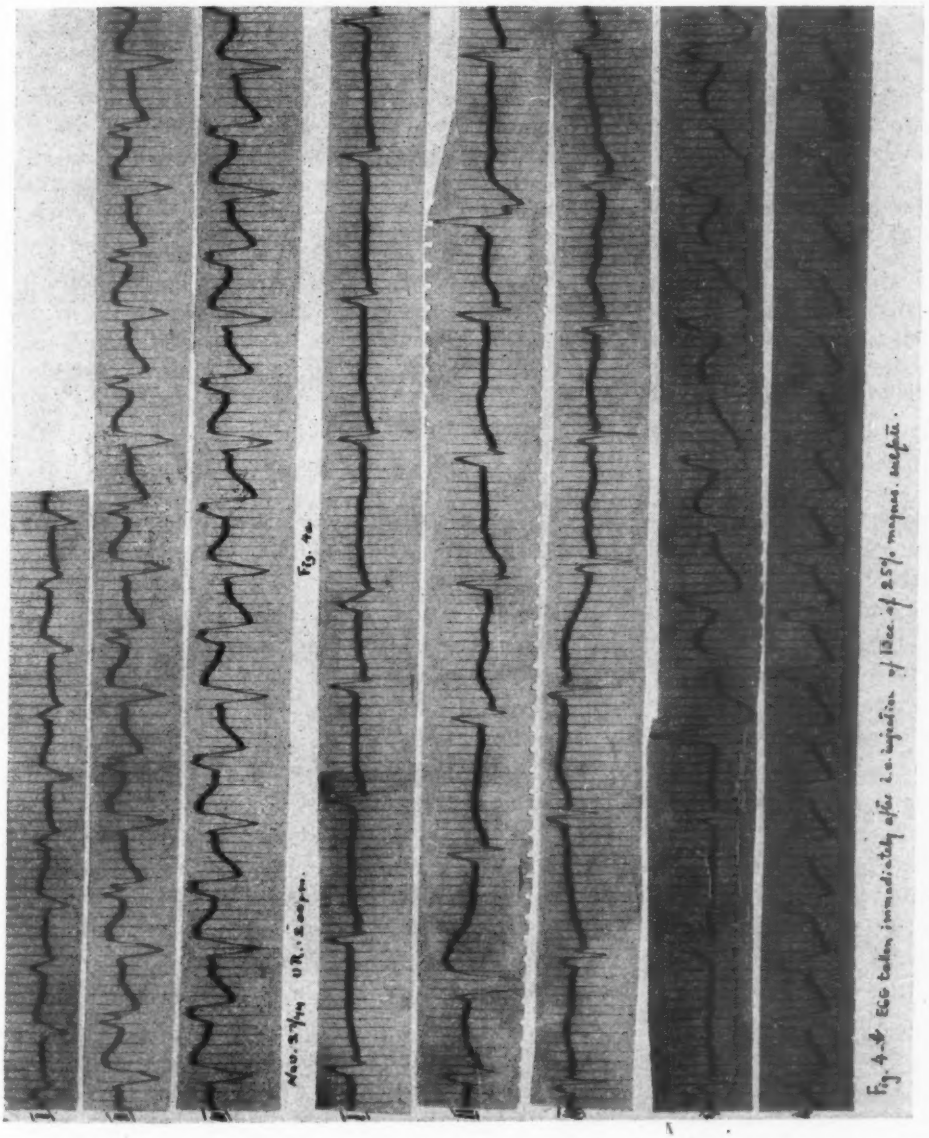

Fig. 4.

During the electrocardiographic registration she was seized with a sudden attack of ventricular tachycardia which lasted about ten minutes (Fig. 3, *e*). Carotid sinus and ocular pressure did not affect the paroxysm. The attack subsided suddenly. An electrocardiogram made after the attack showed a low T wave in Lead II, and a slight inversion of the T wave in Lead III which became more distinct on the following day (Fig. 3, *d*).

During the following ten days, during which she was hospitalized, the patient was given estradiol intramuscularly and 3 grains of quinidine sulfate four times daily. She ex-

perienced no attacks and had no complaints even after an hour's walk. When the patient was seen two weeks later, after discharge from the hospital, she stated that the irregular beats still occurred for short periods and were followed by attacks of rapid palpitation.

During this period she had been taking 3 grains of quinidine sulfate twice daily. This was increased to 9 grains taken as a single daily dose. When seen six weeks later the patient stated that the dose of 9 grains was well tolerated and that she had experienced no further irregular beats.

CASE 4.—The patient, a 57-year-old man, suffered from cardiac failure due to hypertensive heart disease. Cheyne-Stokes breathing, hydrothorax, edema, and auricular fibrillation were present. He was extremely sensitive to digitalis. Even a single dose of 1½ grains caused nausea and vomiting. When he was given 1½ grains twice daily, he developed a sudden attack of tachycardia which the electrocardiogram showed to be of ventricular origin and which was characterized by alternating direction of the ventricular complexes (Fig. 4, *a*). Intravenous injection of 10 c.c. of 25 per cent magnesium sulfate stopped the attack. However, after approximately three minutes the tachycardia reappeared. For a brief period the ventricular complexes were bidirectional. Soon, however, the ventricular beats became unidirectional (Fig. 4, *b*). Digitalis was discontinued and 9 grains of quinidine were given orally. The attack stopped after two hours. During the following seven days, 3 grains of quinidine were given once daily. The attack did not reappear. The patient improved gradually, and when last observed, six months after the original seizure, was in fairly good condition.

DISCUSSION

The striking feature of the clinical picture in Case 1 was the complete absence of serious distress during the twenty-six days of the paroxysm. In spite of the long duration of the attack there were no signs of heart failure. There is a general impression that a severely injured heart cannot long maintain a ventricular rate of 150 to 200. However, Fishberg[17] emphasizes that in a vast majority of attacks of paroxysmal tachycardia, even in those with a rate above 200, there are no signs of circulatory failure. After cessation of the attack the electrocardiogram showed the characteristic tracing of posterior myocardial infarction. The occurrence of ventricular tachycardia with myocardial infarction is not uncommon, but it is usually associated with a recent myocardial lesion. In Case 1, however, the clinical and laboratory findings did not give evidence of acute myocardial lesion. The temperature, sedimentation rate, and white blood count were normal. It seems probable, therefore, that the sensitization of ventricular foci by the excessive use of digitalis was responsible for the attack. It is well known that a small dose of digitalis taken over a long period of time may produce a more severe intoxication than a large dose taken for a short time.

In Cases 2 and 3 there was no evidence of cardiac damage. No cause for the attacks could be found, except possibly in Case 3, where an increase in frequency and duration of the attacks was associated with the premenstrual cycle. The patients were 39 and 38 years of age, respectively. Both were able to continue their work after the tachycardia subsided. The electrocardiogram taken after the cessation of the attack in Case 2 showed inverted T waves in Lead I and in the chest leads, and that taken in Case 3 showed inverted T waves in Leads II and III. It was interesting to note that after the attack not only did the T waves in Lead I and in the chest leads become inverted, but the R wave

in the chest leads disappeared. Thus the pattern of the electrocardiogram became similar to that of anterior myocardial infarction (Fig. 2, *b*).

The occurrence of inverted T waves following an attack of paroxysmal tachycardia has been previously described, but opinion as to the interpretation of this phenomenon is still not uniform. In Cases 2 and 3 the inverted T waves disappeared after ten days and three weeks, respectively, and the electrocardiograms became normal. The short duration of the abnormal electrocardiograms suggests that they are due to myocardial ischemia caused by the paroxysmal attack. The absence of the R wave in the chest leads indicates that the ischemia affected the anterior wall.

The ventricular tachycardia with alternating form of the ventricular complexes, noted in Case 4, usually occurs in patients who have severe myocardial damage and are under digitalis therapy.[1, 2, 19, 20, 22, 23] It is generally considered a fatal condition; in fact, in all the reported cases except one,[23] death has occurred either during the attack or within a short period thereafter.

Various explanations of the mechanism of the alternating form of paroxysmal ventricular tachycardia have been offered. One theory is that two independent foci, one in each ventricle, alternately initiate the contractions. According to another theory, the cardiac impulse arises in a single focus situated at the bifurcation of the bundle of His and, due to a defect in the bundle branches, the impulse is transmitted alternately over the right and left branches, thereby producing the picture of bundle branch block.[2, 19, 20] The possibility of a double ventricular circus movement has also been suggested.[21]

The absolute regularity of the rhythm in these tachycardias leads us to favor the theory of a single focus, since the assumption that two independent foci are present would make it difficult to explain the regular rhythm.[20] Scherf and Kisch,[22] in a careful analysis of their cases, have been able to demonstrate that the stimuli originate in one center and that the change in the form of the ventricular complexes is due to disturbance of the intraventricular conduction. The regular rhythm in the paroxysmal tachycardia supports the view of a single focus with impairment of the bundle branch conduction.

TREATMENT

Although the value of quinidine sulfate in the treatment of attacks of paroxysmal tachycardia is generally recognized, there is still some difference of opinion with regard to its usefulness, the dosage, and the mode of administration.[6, 8, 18] The usual dose varies between 5 and 15 grains, given orally at intervals of two or three hours. Rarely is a single dose exceeding 20 grains recommended, although a single dose of 40 grains has been reported.[10] If oral administration remains ineffective, intramuscular or intravenous injection of quinidine dihydrochloride is recommended. Intramuscular injection of quinidine dihydrochloride was without effect in Case 1. However, Riseman and Linenthal[11] report that it is helpful in cases in which vomiting or poor absorption from the gastrointestinal tract is present.

In view of the extreme danger and risk attending the intravenous injection of quinine, it is advisable to abandon this method of administration. In

fact Paul White[18] emphasizes that "it is simpler, safer, and probably almost as effective to give quinidine by mouth." Our experience in this case and that of others in recently reported cases seems to indicate that a large, single dose is more useful than a great amount of quinidine given in smaller doses over a longer period of time.

SUMMARY

Four cases of paroxysmal ventricular tachycardia are reported. One attack lasted for twenty-six days without interruption and, although associated with myocardial infarction, ended with complete recovery after oral administration of a large, single dose of quinidine sulfate. Another attack, which showed bidirectional ventricular complexes due to digitalis intoxication, was treated in this manner, and recovery followed. In two of the four cases there was no evidence of organic heart disease.

The electrocardiographic changes associated with and following a paroxysm of ventricular tachycardia are discussed.

The advantage of oral administration of a large, single dose of quinidine sulfate is emphasized.

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ELECTROCARDIOGRAPHIC STUDIES DURING AND AFTER PNEUMOCOCCUS PNEUMONIA

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REPORTED studies show that pneumonia may be accompanied by electrocardiographic deviations from the "normal."[1-4, 6] These include changes in the heart rate and rhythm as well as significant variations in the P wave, T wave, RS-T segment, and various components of the QRS complex. The recorded incidence of such changes has varied widely, apparently depending on such factors as selection of cases, severity of pneumonia, time of study in relation to the course of the disease, and length of observation. The reported incidence of T-wave inversion in Leads I and II of the electrocardiogram has varied between 2.4 per cent[3] and 27.1 per cent.[6] Significant P-R interval prolongation has varied between 6.9 per cent[3] and 35 per cent.[2] In some instances, the electrocardiographic changes were such that they were interpreted as being due to myocardial disease.[2-4, 6] The electrocardiographic studies reported thus far have been based almost entirely on tracings obtained from the standard leads.

In this study, which is a part of a general study of the circulation in pneumococcus pneumonia,[7] the precordial Lead IVF[8] was recorded as well as the standard limb leads. Serial electrocardiograms including standard and chest leads were made routinely on pneumonia patients upon admission to the hospital and at frequent intervals during the disease and after recovery. Each record was taken with the patient in the supine position at an angle of about 30 degrees with the horizontal. In order to keep the chest electrode at a constant point for serial examinations, its position was marked by the intracutaneous injection of the blue dye, T-1824, which remains at the site of injection for several weeks.

This report is based upon a study of 449 electrocardiograms. Four hundred and thirty of these tracings were made on 82 patients who survived pneumonia and who had at least one electrocardiogram taken during the disease and one after recovery (the number per patient varied between two and 16). Nineteen of the electrocardiograms were made on 10 patients who died of pneumonia. Each of the patients in the study had pneumococcus pneumonia, proved bacteriologically by study of sputum and blood. In each instance the clinical diagnosis and location of the pulmonary lesion was confirmed by x-ray or autopsy. It is emphasized that these cases differ somewhat

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from those previously reported in the literature in that most were seen early in the course of pneumonia, the average duration of disease at the time of admission being three days; and each was treated by either type-specific antipneumococcus serum, or chemotherapy, or both. The total febrile course was characteristically short, averaging slightly over four days in those cases in which the onset of disease and the crisis could be precisely defined. These factors may account, in part, for the discrepancies between previous observations and those reported here.

The following patients were excluded from the study: all those with single electrocardiographic observations; four who, during intravenous therapy, developed electrocardiographic abnormalities which persisted on recovery from pneumonia and were thought to be a result of such therapy[9]; and two patients who, during pneumonia, developed electrocardiographic changes which persisted on recovery and were associated with clinical and laboratory manifestations of acute rheumatic fever. Included in the group are those patients who developed temporary electrocardiographic changes during intravenous therapy which apparently were unrelated to the pneumonia. These temporary alterations associated with intravenous therapy are, however, not included as changes due to pneumonia and have been reported elsewhere.[9] Digitalis was administered to two patients. Both died and are included in the series of fatal cases.

Although in this study the most striking changes occurred in the T waves, other minor electrocardiographic deviations, such as sinus tachycardia, postcritical bradycardia, and insignificant changes in the RS-T segment were encountered. The RS-T segment changes usually consisted of deviation from the base line of 1 mm. or less. Disturbances in the basic cardiac rhythm were not observed during the course of pneumonia. A significantly abnormal P-R interval, that is, a P-R that was greater than 0.21 second or one that showed a change of ± 0.04 second in serial tracings, was not observed in any patient.

TABLE I. ELECTROCARDIOGRAPHIC CHANGES OTHER THAN T-WAVE CHANGES IN NINETY-TWO PATIENTS DURING PNEUMOCOCCUS PNEUMONIA

	RECOVERED		DIED	
	NUMBER	PER CENT	NUMBER	PER CENT
Tachycardia (rate > 125)	12	14.7	4	40.0
Postcritical bradycardia (rate < 60)	8	9.8	–	–
P-R interval > 0.21 second or change ± 0.04 second	–	–	–	–
Change in RS-T interval ± 1 mm. or less	9	11.1	1	10.0
Change in axis deviation*	17	20.7	–	–
Total cases observed	82	100.0	10	100.0

*Toward right during pneumonia (11 cases; 13.4 per cent); toward left during pneumonia (6 cases, 7.3 per cent).

TABLE II. INCIDENCE OF T-WAVE CHANGES IN NINETY-TWO PATIENTS WITH PNEUMOCOCCUS PNEUMONIA AT THE TIME OF ADMISSION TO HOSPITAL ACCORDING TO OUTCOME OF THE DISEASE

	NUMBER			PER CENT	
	TOTAL	T-WAVE CHANGE	NO T-WAVE CHANGE	T-WAVE CHANGE	NO T-WAVE CHANGE
Recovered—no permanent change	70	23	47	57.5	90.4
—permanent T-wave change	12	12	–	30.0	–
Died	10	5	5	12.5	9.6
Total cases observed	92	40	52	100.0	100.0

Changes in axis deviation occurred in a few instances. The electrocardiographic changes other than significant T-wave changes are summarized in Table I.

Changes in the T waves were noted on admission in 35 of 82 patients (42.7 per cent) who survived pneumonia, and in five of the 10 patients who

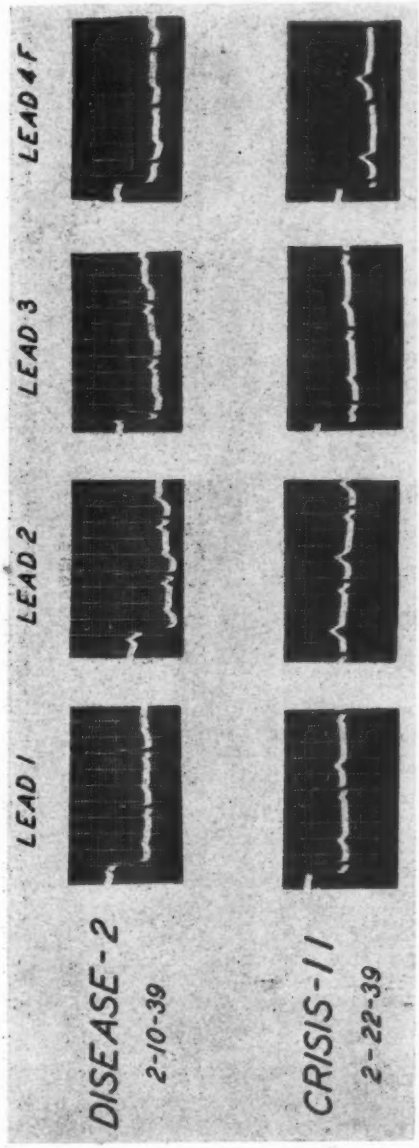

Fig. 1.—Woman, aged 50 years. Electrocardiograms taken on the second day of pneumococcus pneumonia, Type VII, and eleven days after crisis. No bacteremia. Right middle lobe involved. History of angina pectoris.

died (Table II). These changes consisted chiefly of low amplitude T waves (2 mm. or less), or inversion of the T waves, or both, in Leads I, II, and IVF (Table III). Deviations in T_3 alone were not considered significant in this study. In the 12 patients in whom the T-wave changes persisted upon recovery

from pneumonia, it is believed that underlying myocardial disease was their cause. However, in 23 (28.1 per cent) of the patients who survived pneumonia, electrocardiographic changes suggestive of "myocardial disease" occurred during the disease and disappeared during recovery. In no instance did a pneu-

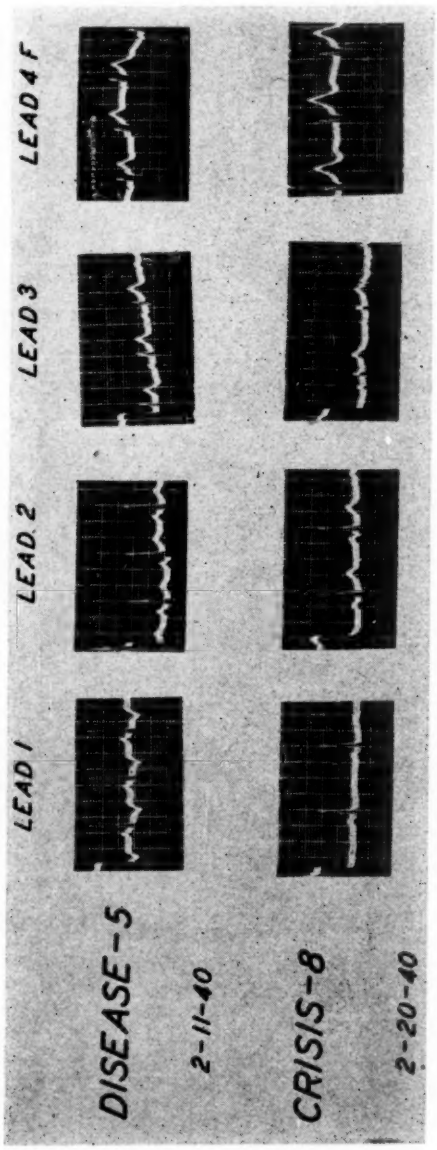

Fig. 2.—Woman, aged 62 years. Electrocardiograms taken on the fifth day of pneumococcus pneumonia, Type II, and eight days after crisis. No bacteremia. Right and left lower lobes involved. Pleural effusion developed at left base on twelfth day after crisis.

monia patient with a normal electrocardiogram at the time of admission to the hospital develop transient T-wave changes of the type here described while under observation.

Figs. 1 to 4 illustrate characteristic examples of the transient electrocardiographic abnormalities encountered in pneumonia. It will be noted that although T-wave inversions occurred they were not accompanied by significant

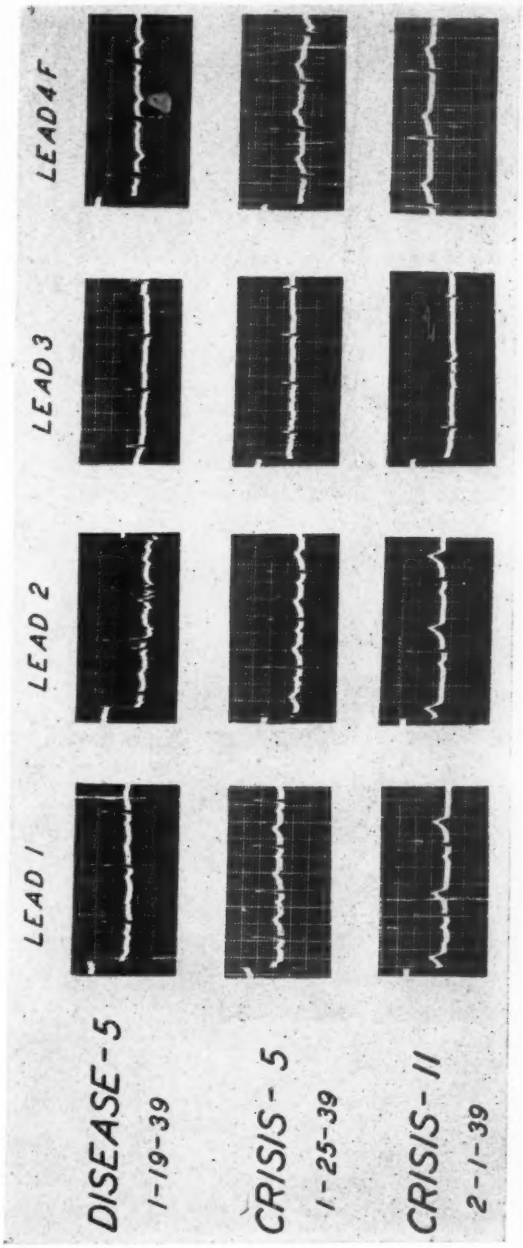

Fig. 3.—Girl, aged 18 years. Electrocardiograms taken on the fifth day of pneumococcus pneumonia, Type VI, and five and eleven days after crisis. Right lower lobe involved. No bacteremia. No evidence of heart disease.

alterations in the RS-T segment. Furthermore, the trend of T-wave changes which occurred during the course of pneumonia was consistent and followed a definite pattern; during the acute phase of the disease the T waves were flat

or inverted; and as the patients recovered from their disease the T waves returned toward, or to, normal.

Two patients developed classic evidence of acute myocardial infarction during pneumonia. The electrocardiograms of one of them are shown in Fig.

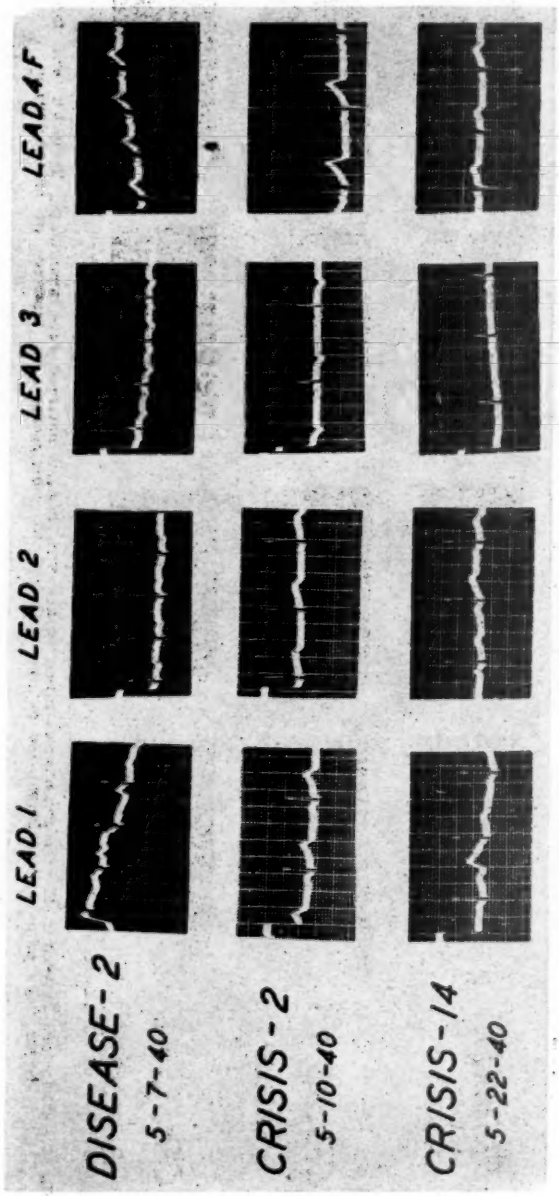

Fig. 4.—Boy, aged 14 years. Electrocardiograms taken on the second day of pneumococcus pneumonia, Type I, and two and fourteen days after crises. Right lower lobe involved. No bacteremia. No evidence of heart disease.

5 to emphasize the contrast between this electrocardiographic pattern and that due to pneumonia alone, particular emphasis being placed on the lack of significant RS-T segment change in the latter. Both patients recovered

and are included in the group of recovered patients having permanent electrocardiographic changes.

One patient was observed during two attacks of lobar pneumonia involving the right upper lobe (Figs. 6*A* and 6*B*). During the first attack a Type I

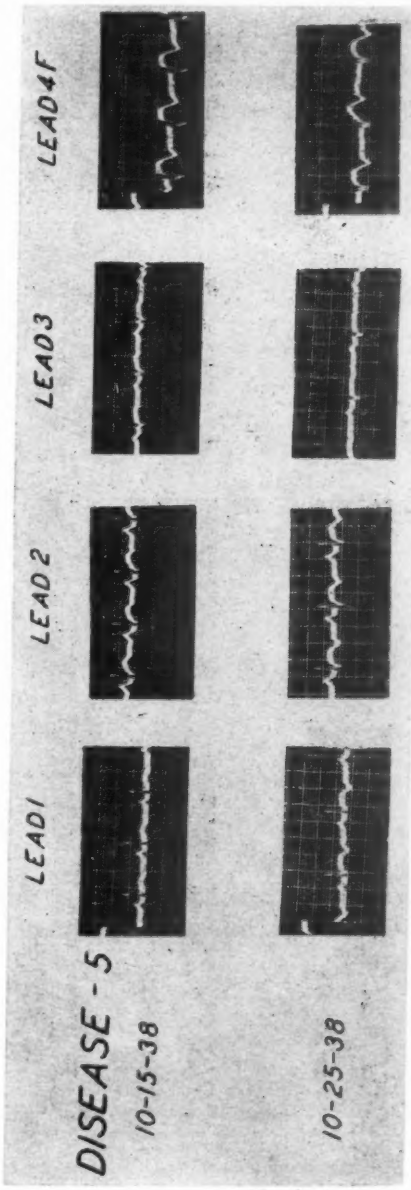

Fig. 5.—Man, aged 58 years. Electrocardiograms taken on the fifth and fifteenth days of pneumococcus pneumonia, Type VII. Right lower lobe involved. No bacteremia. Acute anterior myocardial infarction. Note significant changes in RS-T segment in contrast to changes observed in the electrocardiograms in Figs. 1, 2, 3, 4, and 6.

Pneumococcus was recovered from the sputum; during the second attack a Type VIII *Pneumococcus* was recovered from both sputum and blood. The first attack was treated with Type I antipneumococcus rabbit serum; the second attack was

treated with oral sulfapyridine (total dose 24 Gm). It is of interest to note that similar deviations in the electrocardiogram occurred during both attacks of pneumonia and that there was a return to normal on recovery in each instance.

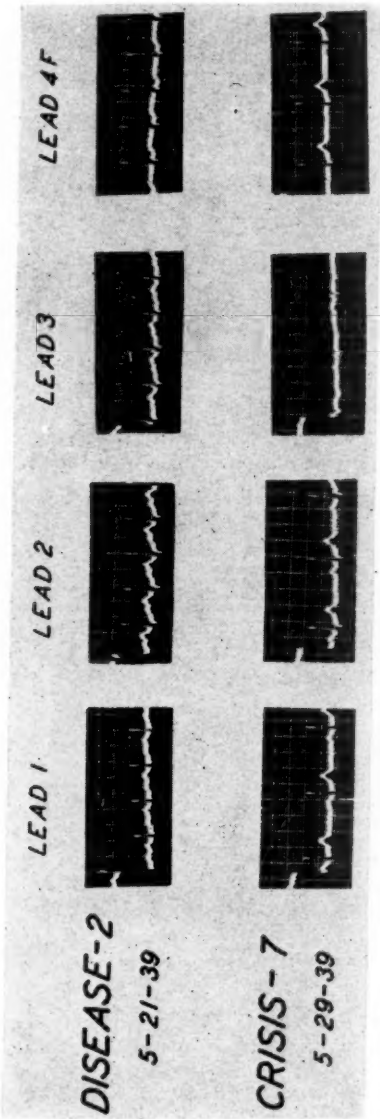

Fig. 6A.—Woman, aged 38 years. Electrocardiograms taken during two attacks of pneumococcus pneumonia involving the right upper lobe. *A*, The first attack was caused by pneumococcus Type I. No bacteremia.

Table IV summarizes the specific therapy employed in the recovered cases. It will be seen that the electrocardiographic changes are independent of the types of treatment employed: type-specific antipneumococcus serum, sulfonamide given orally or parenterally, or combinations of these forms of therapy.

In order to determine what factors might induce transient electrocardiographic changes in some cases of pneumonia but not in others, various possible factors, including age, sex, type of pneumococcus, bacteremia, occurrence of pleural fluid, location of lesion, chest pain, heart rate, and the presence of pre-

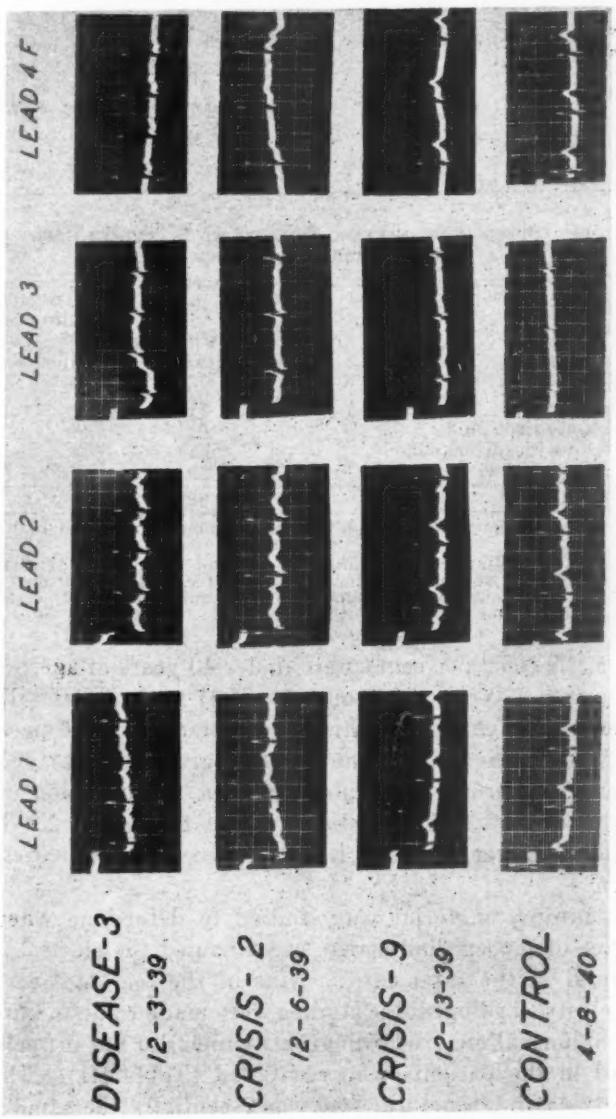

Fig. 6B.—The second attack was caused by pneumococcus Type VIII. Bacteremia present. No evidence of heart disease. Note the identical electrocardiographic changes during each attack of pneumonia with return to normal on recovery.

existing cardiovascular disease, were analyzed. These are summarized in Table V. Except possibly for age, no significant correlation could be demonstrated. It is of interest to note that T-wave changes occurred most frequently in relatively young individuals who presented no other evidence of cardiovascular disease. Of 23 patients showing transient electrocardiographic changes

TABLE III. T-WAVE CHANGES IN NINETY-TWO PATIENTS WITH PNEUMOCOCCUS PNEUMONIA

	RECOVERED		
	TRANSIENT CHANGES (23 PATIENTS)	PERMANENT CHANGES (12 PATIENTS)	DIED (5 PATIENTS)
Low voltage T_1	11	4	4
Low voltage T_2	8	3	2
Low voltage T_4	1	0	0
Inverted T_1	1	1	0
Inverted T_2	4	1	1
Inverted T_4	3	1	1
Diphasic T_1	0	2	0
Diphasic T_2	0	0	0
Diphasic T_4	6	5	0

TABLE IV. SPECIFIC THERAPY IN EIGHTY-TWO RECOVERED CASES OF PNEUMOCOCCUS PNEUMONIA

TREATMENT	NUMBER OF CASES TREATED	NUMBER OF CASES SHOWING TEMPORARY T-WAVE CHANGES DURING PNEUMONIA
Serum alone	30	7
Sulfonamide alone	31	8
Both serum and sulfonamide	21	8
Serum alone or with sulfonamide	51	15*
Sulfonamide alone or with serum	52	16†
Total recovered cases	82	

*Of these, nine received horse serum, five received rabbit serum, and one received both horse and rabbit serum.

†Of these, 13 received sulfapyridine (total dose ranging from 8 to 52.5 Gm.); two received sulfathiazole (total dose 20 and 25.5 Gm.); and one received both drugs. Sulfonamides were administered by intravenous route in nine cases; sodium sulfapyridine, in eight cases (dose range 3.8 to 7.6 Gm.); and sodium sulfathiazole in one case (dose 3 Gm.).

during pneumonia, 15 (65.2 per cent) were under 40 years of age. The average age for the group was 37 years. In contrast, of 47 patients who did not show any electrocardiographic changes during pneumonia, 28 (59.6 per cent) were over 40 years of age. The average age in this group was 44 years. In the cases with transient electrocardiographic changes, the duration of the pneumonia at the time the first electrocardiogram was taken was 2.9 days, and in those without such changes, it was 3.1 days. Anoxia in the two groups will be discussed later.

Finally, the autopsy material was studied to determine whether or not pathologic evidence of myocardial change accompanied the electrocardiographic abnormalities found in the fatal cases. Nine of the ten fatal cases of pneumonia on whom electrocardiographic studies were made came to autopsy. Five of these showed abnormal electrocardiograms which did not differ appreciably from those found in the patients who recovered (Table III). The incidence of abnormal electrocardiograms likewise was essentially the same in the fatal and nonfatal cases (Table II). In the four patients without electrocardiographic changes and in four of the five patients with abnormal electrocardiograms, there was no significant gross or microscopic evidence of heart disease. In one patient, in whom the electrocardiogram showed inverted T waves in Leads II and III, an acute fibrinous pericarditis was found which could have accounted for the T-wave changes. Although digitalis was given to two

TABLE V. T-WAVE CHANGES OCCURRING IN EIGHTY-TWO RECOVERED CASES OF PNEUMOCOCCUS PNEUMONIA ACCORDING TO CERTAIN FACTORS IMPORTANT IN PNEUMONIA

		T-WAVE CHANGES					
		NUMBER			PER CENT		
	TOTAL	TRANSIENT	PERMANENT	NONE	TRANSIENT	PERMANENT	NONE
Age							
Less than 40 years	38	15	4	19	65.2	33.3	40.4
40 years and over	44	8	8	28	34.8	66.7	59.6
Sex							
Male	40	13	5	22	56.5	41.7	46.8
Female	42	10	7	25	43.5	58.3	53.2
Pneumococcus Type							
Common (I, III, V, VII, and VIII)	44	14	8	22	60.9	66.7	46.8
Other types	38	9	4	25	39.1	33.3	53.2
Bacteremia							
Present	15	6	3	6	26.1	25.0	12.8
Absent	67	17	9	41	73.9	75.0	87.2
Pleural Fluid							
Present	9	5	1	3	21.7	8.3	6.4
Absent	73	18	11	44	78.3	91.7	93.6
Location of Lesion in Lung							
Right only	53	13	10	30	56.5	83.3	63.8
Left only	21	6	2	13	26.1	16.7	27.7
Both	8	4	–	4	17.4	0.0	8.5
Chest Pain							
Present	64	18	8	38	78.3	66.7	80.9
Absent	16	4	4	8	17.4	33.3	17.0
Not known	2	1	–	1	4.3	0.0	2.1
Heart Rate							
Under 125	70	20	11	39	87.0	91.7	83.0
125 and over	12	3	1	8	13.0	8.3	17.0
Pre-existing Cardiovascular Disease							
Present	6	2	2	2	8.7	16.7	4.3
Absent	68	19	7	42	82.6	58.3	89.3
Uncertain	8	2	3	3	8.7	25.0	6.4
Total recovered cases	82	23	12	47	100.0	100.0	100.0

patients in this group (total dose 0.5 and 0.7 Gm., respectively) the changes in their electrocardiograms were not characteristic of digitalis effect and the autopsy findings (in them) were not significantly different from the autopsy findings in patients who had not received digitalis.

The appearance of such T-wave changes as are here described raises the question of whether or not they represent evidence of "myocarditis." Autopsy studies of the hearts, of pneumonia patients, made before 1917, were reviewed by Cohn and Jamieson.[1] These failed to show the presence of significant myocardial changes in pneumonia and led the authors to state: "Of the pathologic histology of the heart in pneumonia there is still insufficient knowledge, but it does not appear that extensive alterations occur. Anatomical lesions are according to these investigations infrequent and on the whole insignificant." In contrast, Stone[10] more recently reported observations on 34 cases of lobar pneumonia in which abnormalities in the myocardium were found in 79.4 per cent, by histologic examination. Included in the pathologic diagnoses were "parenchymatous degeneration" (52.9 per cent), "fatty degeneration" (11.7 per cent), "leucocytic and round cell infiltration" (8.9 per cent), "hyaline degeneration" (2.9 per cent), and "interstitial myocarditis" (2.9 per

cent). The significance and interpretation of such changes, however, are open to question and are not supported by the autopsy findings in the present study.

The observation that myocarditis may be associated with sulfonamide administration[11, 12] focuses attention on the possible role played by sulfonamide therapy in the production of the type of electrocardiographic changes which were observed in this study. Analysis of the cases failed to show a preponderance of electrocardiographic changes in the sulfonamide-treated cases as compared with the nonsulfonamide-treated cases (Table IV). Against a relationship between the drug and the electrocardiographic changes is the fact that in this study abnormal electrocardiograms were found in the patients at the time of admission to the hospital, before sulfonamides were administered. Furthermore, the administration of these drugs did not appear to alter the subsequent course of the electrocardiogram. Finally, in the nine fatal cases with electrocardiographic changes which came to autopsy, eight of which received one or more of the sulfonamide drugs, evidence of myocarditis, as described by French and Weller,[11] was lacking. It is not possible, therefore, to ascribe the electrocardiographic changes which were found in pneumonia in this study to recognizable structural abnormalities of the myocardium which were a result of either pneumonia or sulfonamide administration.

Since anoxia is capable of producing T-wave changes similar to those reported here,[13] blood-gas studies were made to obtain information on this point. At the same time that electrocardiograms were taken (on admission and after recovery) arterial oxygen content and capacity were determined in 33 cases, and arterial carbon dioxide content was determined in 32 cases. The mean arterial oxygen saturation during pneumonia was somewhat reduced, being 92.1 per cent in patients showing transient T-wave changes and 89.9 per cent in those without such electrocardiographic changes. Individual cases, however, showed considerable variation: from 78.3 per cent to 101 per cent in those with transient T-wave changes, and from 91.4 per cent to 99.3 per cent in the cases without such electrocardiographic changes. Similarly, the arterial carbon dioxide content did not show significant differences in the two groups: in the patients who showed transient T-wave changes it varied from 31.4 to 51.3 volumes per cent, with a mean of 42.2 volumes per cent; in those without such electrocardiographic changes it varied from 33.5 to 55.3 volumes per cent, with a mean of 43.5 volumes per cent. After recovery from pneumonia, both the oxygen saturation and the carbon dioxide content of the arterial blood in both groups were usually slightly, but about equally, increased as compared with the determinations made during the course of pneumonia. These observations lend little support to the concept that anoxia is causally related to the T-wave changes which occur during pneumonia. In this regard, however, the observation of May,[14] that the more normal the myocardium the more susceptible it is to induced anoxia (as evidenced by T-wave change), is of speculative interest. It has already been emphasized that the patients in this study who showed transient T-wave changes in the electrocardiogram were for the most part relatively young, and free from cardiovascular disease (Table V).

Certain factors which are considered of importance in pneumonia and which might be associated with the electrocardiographic abnormalities encountered in this study were analyzed. Such analysis failed to show positive correlation between T-wave changes and bacteremia, location of lung lesion, presence or absence of pleural fluid, chest pain, or duration of disease (Table V). Although fever has been reported as a cause of electrocardiographic deviations somewhat similar to those reported here,[15] our data showed no differences in the febrile response between the patients with and those without electrocardiographic changes. The patients showing electrocardiographic changes had a mean temperature of 103° F. at the time the admission electrocardiogram was taken, whereas those showing no electrocardiographic changes had a mean temperature of 102.9° F. at the time the admission electrocardiogram was taken.

It seemed possible that circulatory changes, such as increased plasma volume,[7] which are known to occur during pneumonia, might play a role in the production of transient T-wave changes by placing an additional burden on the heart. Analysis of these data,[7] however, showed that in twelve patients with T-wave changes during pneumonia the mean increase in plasma volume during pneumonia was 272 c.c. (13 per cent), whereas in twenty-four patients in whom such electrocardiographic changes did not occur during pneumonia the mean increase in plasma volume was 328 c.c. (11.4 per cent).

The altered electrolyte balance in pneumonia, particularly the shifts in sodium and potassium concentration, may also play a role. No data are available from this study to support or refute this possibility.

Various investigators have pointed out the serious prognostic significance in pneumonia of certain electrocardiographic changes, particularly low voltage T waves and T wave inversion. Master, Romanoff, and Jaffee[2] stated that "negative T waves may be significant of an extremely toxic and fatal pneumonia" and, to substantiate this view, reported a mortality of 40 per cent in a group of patients with such changes, in contrast with a mortality of 17 per cent in a control group. Bullowa and Lowen,[6] supporting this contention, reported a 46 per cent mortality in cases with flat or inverted T waves, in contrast with a 10 per cent mortality in a group of pneumonia patients who did not show this change. Bellet and McMillan[5] expressed the opinion that, in pneumonia, manifestations of severe myocardial derangement, such as T-wave inversion, indicated a poor prognosis. In this study, however, alterations in voltage, or even inversion of the T waves in Leads I, II, and IVF, with or without minor RS-T segment changes, when due to pneumonia, were not found to be of serious prognostic importance in a group of patients with pneumonia who were treated adequately (Table II).

Although this study has not thrown light on the mechanism of production of the transient T-wave changes which occur during pneumonia, it is important to recognize that T-wave changes such as are here described may accompany pneumonia, disappear on recovery from this disease, and not be due to significant structural changes in the myocardium. This fact is of importance

in assessing the cardiac status of patients who present evidences of acute pulmonary infection and electrocardiographic abnormalities such as have been described. In the absence of "classic" electrocardiographic evidence of myocardial infarction, electrocardiograms taken during pneumococcus pneumonia must be interpreted with caution and with due consideration of the changes which pneumonia per se may produce. The final diagnosis of the cardiac status of such patients must await interpretation of postrecovery electrocardiograms. Failure to do this may lead to erroneous diagnoses of "myocardial disease."

SUMMARY AND CONCLUSIONS

1. Deviations from normal are frequently found in electrocardiographic tracings taken during pneumococcus pneumonia.

2. T-wave changes of sufficient degree to suggest "myocardial disease" occurred in 35, or 43 per cent, of a carefully studied group of 82 patients who survived pneumococcus pneumonia. In 23 patients, or 28.1 per cent of the total group, these changes followed a definite pattern during the disease and disappeared on recovery.

3. Post-mortem examination of the hearts of nine patients who died of pneumococcus pneumonia showed no significant structural abnormality, even though four of these showed T-wave changes in the electrocardiogram. In one patient whose electrocardiogram showed T-wave inversion an acute fibrinous pericarditis was present.

4. Flat, low-voltage, or inverted T waves in Leads I, II, or IVF, without significant S-T changes, occurring during, and related to the pneumonia, are not of serious prognostic importance if the pneumonia is diagnosed early and treated adequately.

5. Recognition of the occurrence of transient T-wave changes in pneumococcus pneumonia may be of importance in the differential diagnosis of pneumococcus pneumonia and myocardial disease in patients in whom clinical evidence is not definitive.

6. The possible causes of such electrocardiographic changes are discussed.

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CALCIFICATION OF THE MITRAL VALVE

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THE frequent observation by roentgenologists and pathologists of calcification in the region of the mitral valve has led to much conjecture concerning its origin and significance. Views regarding its etiology may be divided into three general groups: inflammation, degeneration, and metabolic disturbances. Calcification of the mitral ring has been ascribed to degenerative[1, 7, 8, 10, 11] or atheromatous processes[2, 3] of nonrheumatic origin[6-11] occurring chiefly in the aged.[2, 4, 5, 7, 8, 10, 11] It has been pointed out that the lesion occurs at the site of maximum stress and strain[1] and that decreased blood supply is an important factor in its genesis. Others have suggested a similarity to the Mönckeberg type of aortic valve calcification,[12, 13] assuming a predilection to collagen involution with deposition of lipoid and calcium.[12] The acellular structure of the posterior portion of the annulus is held responsible for localization of calcification in that part of the ring.[20] Many investigators are of the opinion that calcification of the annulus fibrosus of the mitral valve is of no clinical significance. On the other hand, calcification of the leaflets of the mitral valve has been considered inflammatory (rheumatic) in origin, when it occurs in younger age groups.[3, 6, 7, 9, 10]

Decreasing the caloric intake in rats has been found to result in increased calcium deposition in the heart, the aorta, and the kidneys.[14] Animal experimentation has also shown that the form of mineral supplement has an effect upon the production of cardiac calcification, but that moderate enforced exercise reduces the incidence of calcification.[15] The present investigation was undertaken to determine the incidence and distribution of calcification on the mitral valve and to evaluate its clinical significance.

METHOD OF STUDY

Seven hundred sixty-six unselected hearts, prepared by the Schlesinger technique,[16] were used. There is no overlapping of the valve rings and leaflets of the "completely unrolled hearts" prepared by this method, and roentgenograms of these specimens are ideally suited for the detection of areas of calcification which might be overlooked by other methods of examination. The roentgenograms were examined for valvular calcification without reference to pathologic or clinical data. Calcium deposits were recognized as opaque areas in the region of the valve. These deposits appeared as thick heavy bands, light thin lines, or irregular spotty areas. When the deposition occurred as a straight line, or as a U- or J-shaped configuration, the annulus fibrosus was considered

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the site of involvement. Leaflet depositions appeared as spotty areas which were irregularly placed in the region of the mitral valve, in contrast to the continuous bandlike depositions indicating annulus fibrosus involvement. The major difficulty encountered was in distinguishing lighter ring deposits from spotty leaflet involvement. Nevertheless, this technique is more precise than fluoroscopic examinations in vivo, and is far more accurate for detecting minimal calcium deposits than is gross pathologic observation. The pathology protocols and clinical records were then reviewed, and the desired data were tabulated. Since the coronary arteries were injected and dissected,[16] the data pertaining to pathology in the coronary arteries, as well as to calcification in the mitral valve, are considered highly accurate. The "T" test was used in analyzing these data; the results, as given, are significant.

RESULTS

Calcification in the mitral valve was found in 78 hearts, and in approximately one-half of these the aortic valve was similarly involved. The annulus fibrosus was the most frequent site of calcification in the mitral valve, and was involved in 70 of the 78 hearts; in 6 of these there was concomitant calcification of the mitral leaflets. Calcification of the leaflets alone was noted in only 8 hearts. Deposition of calcium occurred almost equally in the anterior and posterior leaflets, while calcification of the annulus fibrosus was more frequently posterior than anterior (Table I). Calcification of the mitral valve was found twice as often in women as in men (Table II), despite a 3:2 ratio of male hearts to female hearts in the entire group of 766 hearts.

TABLE I*A*. SEX, AGE, HEART WEIGHT, AND LOCATION OF CALCIFICATION IN SEVENTY-EIGHT CASES WITH MITRAL VALVE CALCIFICATION

	NUMBER OF CASES	SEX*		AGE (YRS.)		HEART WEIGHT (GRAMS)	
		M.	F.	RANGE	AVERAGE	RANGE	AVERAGE
I. *Mitral Valve Alone*							
1. Annulus alone	29	6	23	35-83	70	268- 900	452
2. Annulus and leaflets	2	1	1	45-61	53	390- 600	495
3. Leaflets alone	5	3	1	28-52	40	510- 825	664
4. Total	36	10	25	28-83	66	268- 900	481
II. *Mitral and Aortic Valves*							
1. Annulus alone (mitral)	35	13	22	44-83	67	180- 780	448
2. Annulus and leaflets (mitral)	4	1	3	28-68	54	350- 560	468
3. Leaflets alone (mitral)	3	2	1	16-68	51	350-1,100	683
4. Total	42	16	26	16-83	65	180-1,100	468
III. *Groups I and II Combined*							
1. Annulus alone	64	19	45	35-83	69	180- 900	450
2. Annulus and leaflets	6	2	4	28-68	54	350- 600	477
3. Leaflets alone	8	5	2	16-68	44	350-1,100	671
Grand total	78	26	51	16-83	65	180-1,100	470

*Not stated in one case.

TABLE I*B*. Location of Calcification on Annulus and on Leaflets of Mitral Valve

	ANNULUS	LEAFLET
Anterior	11	5
Posterior	30	6
Anterior and posterior	29	3

TABLE II. RELATION BETWEEN LOCATION OF MITRAL CALCIFICATION, AVERAGE LIFE SPAN, AND AVERAGE HEART WEIGHT

	MALES			FEMALES		
	NUMBER OF CASES	AGE (YRS.)	HEART WEIGHT (GRAMS)	NUMBER OF CASES	AGE (YRS.)	HEART WEIGHT (GRAMS)
I. *Mitral Valve Alone*						
1. Annulus alone	6	75	427	23	69	460
2. Annulus and leaflets	1	(61)	(390)	1	(45)	(600)
3. Leaflets alone	2	30	668	2	46	690
4. Total	9	63	476	26	66	483
II. *Mitral and Aortic Valves*						
1. Annulus alone (mitral)	14	67	568	22	68	367
2. Annulus and leaflets (mitral)	1	(74)	(350)	3	47	507
3. Leaflets alone (mitral)	1	(16)	(1,100)	1	(67)	(600)
4. Total	16	65	588	26	66	392
Grand Total	25	64	548	52	66	438

The average life span of the 78 patients whose hearts showed mitral valve calcification did not vary significantly with sex or with associated involvement of the aortic valve (Table II). On the other hand, there was a striking correlation between age and the location of calcification. Thus, calcification of the annulus fibrosus alone occurred most frequently in the group of older subjects, whose life span averaged 69 years; while calcification of the mitral leaflets was noted in a younger group, whose life span averaged 44 years (Table I). The average life span of the group whose hearts showed calcification of both the leaflets and the annulus fibrosus is intermediate between that of either group alone.

The weights of the 78 hearts with mitral valve calcification ranged from 180 to 1,100 grams. Concomitant calcification of the aortic valve did not appear to have a significant influence on heart weight. Hypertrophy was present in most cases, but was greatest in those with calcification of a mitral leaflet. The average weight of 8 hearts with only leaflet calcification was 671 grams, while the average weight of 64 hearts with calcification confined to the annulus fibrosus was 450 grams (Table I). This significant difference may be attributed to the preponderance of rheumatic heart disease in the group with leaflet calcification.

Associated Lesions.—Significant cardiovascular disease, other than calcification, was found in over 75 per cent of the 78 hearts (Tables III and IV). Arteriosclerotic and hypertensive heart disease was present in one-third, rheumatic heart disease in one-fifth, myocardial infarction in one-sixth, and bacterial endocarditis in one-twentieth of the cases. Generalized arteriosclerosis was observed in one-half of the cases, and calcification of the coronary arteries was observed in two-thirds. Calcification of both aortic and mitral valves was not associated with a higher incidence of other cardiovascular lesions than when the mitral valve alone was involved.

In cases of valvular calcification with as well as without other cardiovascular disease, the annulus fibrosus was almost always the site of the calcification in the mitral valve. Even in the 15 rheumatic hearts calcification of the leaflets was noted in fewer than half. Three of the 14 hearts with calcification including the leaflets did not have mitral stenosis and two of these three showed none of

TABLE III. INCIDENCE OF VARIOUS CARDIOVASCULAR CONDITIONS IN CASES OF MITRAL VALVE CALCIFICATION IN RELATION TO THE LOCATION OF CALCIFICATION*

	RHEUMATIC HEART DISEASE	BACTERIAL ENDOCARDITIS	ARTERIOSCLEROTIC AND HYPERTENSIVE HEART DISEASE	MYOCARDIAL INFARCTION	GENERALIZED ARTERIOSCLEROSIS	MINIMAL AREAS OF CORONARY CALCIFICATION
I. *Mitral Valve*						
1. Annulus alone	2/28	0/28	11/26	5/26	16/27	22/29
2. Annulus and leaflets	0/2	2/2	0/2	0/2	0/2	0/2
3. Leaflets alone	5/5	0/4	0/5	0/3	0/3	1/5
4. Total	7/35	2/34	11/33	5/31	16/32	23/36
II. *Mitral and Aortic Valve*						
1. Annulus alone (mitral)	6/35	1/35	9/35	7/33	17/33	26/36
2. Annulus and leaflets (mitral)	1/4	1/4	2/4	0/4	2/4	1/4
3. Leaflets alone (mitral)	1/2	0/2	1/2	0/2	0/2	0/2
4. Total	8/41	2/41	12/41	7/39	19/39	27/42
Grand Total	15/76	4/75	23/74	12/70	35/71	50/78

*Discrepancies in the number of cases (denominators) are due to incompleteness of records.

the accepted stigmata of rheumatic heart disease. In all three of these subjects there were hypertension and congestive failure, aortic valve calcification, and extensive coronary disease; the mitral valve calcification involved the annulus as well as the leaflets in two of them. All were women; their ages were 48, 67, and 68 years, respectively. There were, in addition, three other instances of leaflet calcification which were not considered to be rheumatic in origin. These were cases of bacterial endocarditis, two subacute and one acute.

Of 68 cases of mitral valve calcification in which complete pathologic data were available, fifteen, or less than one-fourth displayed no additional cardiac disease other than calcification of the aortic valve, which was present in 10 cases (Table IV). The calcification of the mitral valve in these cases was limited to the annulus fibrosus. In all but 5 cases, however, there was generalized extracardiac vascular disease, i.e., either arteriosclerosis or hypertension. None had angina pectoris. Congestive heart failure was diagnosed clinically in 4 cases, but the diagnosis was questionable in all of them. A clinical diagnosis of heart disease was made in only 5 of the 15 patients. Of the 5 cases with neither important cardiac nor generalized vascular disease, 3 had calcification of both valves and 2 had calcification of the mitral valve alone. In none of the 5 was there angina pectoris or congestive failure, and in none was a clinical diagnosis of heart disease made; none had murmurs. No cardiac death occurred in this group of 15 patients. Vascular disease was the primary cause of death in 2, and neoplastic disease was the cause of death in more than one-third of the group. One patient died at the age of 44 years, following thyroidectomy, and the remaining 14 patients lived beyond the age of 60 years.

Clinical Features.—Reliable data regarding the presence or absence of murmurs were recorded in 53 cases. A murmur was noted in 36, or approx-

TABLE IV. FIFTEEN CASES OF MITRAL VALVE CALCIFICATION WITHOUT ASSOCIATED CARDIAC PATHOLOGY (FROM SIXTY-SEVEN CASES)*

	AGE (YRS.)	HEART WEIGHT (GRAMS)	GENERALIZED ARTERIO-SCLEROSIS	HYPER-TENSION	MUR-MURS†	ANGINA PECTORIS	CLINICAL DIAGNOSIS OF HEART DISEASE	PRIMARY CAUSE OF DEATH
I. *Mitral Ring Alone*								
1. Posterior	67	370	0	0	0	0	0	Carcinoma
	70	347	+	0	0	0	Arteriosclerotic heart disease; auricular fibrillation; congestive failure	Carcinoma
	79	380	0	0	-	0	0	Diabetes mellitus
2. Anterior	63	330	+	0	0	0	0	Myelogenous leucemia
3. Anterior and posterior	83	290	+	0	0	0	Congestive failure	Carcinoma
II. *Mitral Ring, Aortic Valve*								
1. Posterior (mitral ring)	68	280	0	0	-	0	0	Bronchiectasis
	70	330	0	0	0	0	0	Mesenteric thrombosis
	65	335	0	+	Aortic systolic	0	Aortic stenosis	Meningioma
	81	340	+	0	-	0	0	Meningioma
	73	240	+	0	-	0	Congestive failure	Purulent tracheo bronchitis
	44	330	0	+	-	0	Congestive failure	Postthyroidectomy hemorrhage
2. Anterior	73	180	0	0	0	0	0	Intestinal obstruction
	61	380	+	0	0	0	0	Carcinoma
3. Anterior and posterior	74	330	+	0	-	0	0	Cerebral hemorrhage
	78	215	+	0	-	0	0	Bronchiectasis

*Pathology data incomplete in eleven cases.

†+ = murmur present; 0 = no murmur present; - = no notation concerning murmur.

imately two-thirds of these cases; it was apical in 23, aortic in 5, and was heard at both areas in 8. The apical murmur was diastolic in 9 cases; 7 of these were instances of rheumatic heart disease. Eight of the 13 cases with a murmur over the aortic area had aortic in addition to mitral valve calcification, but 5 did not. Murmurs were regularly present in the rheumatic group, but were present in only slightly more than one-half of the nonrheumatic group. They were, however, heard in 70 per cent of the patients with arteriosclerotic and hypertensive heart disease.

The incidence of hypertension, angina pectoris, and congestive failure was not significantly greater in the cases showing calcification of both the aortic and mitral valves than in those with mitral valve calcification alone (Table V). Congestive failure occurred in 60 per cent, hypertension occurred in 38 per cent, and angina pectoris occurred in 16 per cent of the cases. Angina pectoris did not occur in any case with leaflet calcification, but congestive failure was especially common in this group (80 per cent).

Electrocardiograms were available in 29 patients with mitral valve calcification. In only 2 of these, both of whom had bundle branch block, was the calcification a possible factor in producing an abnormal pattern.

TABLE V. HYPERTENSION, ANGINA PECTORIS, AND CONGESTIVE FAILURE IN CASES OF MITRAL VALVE CALCIFICATION*

	HYPERTENSION	ANGINA	CONGESTIVE FAILURE DIAGNOSED
I. *Mitral Valve Alone*			
1. Annulus alone	12/27	4/27	15/28
2. Annulus and leaflets	0/2	0/2	1/2
3. Leaflets alone	0/4	0/3	3/3
4. Total	12/33	4/32	19/33
II. *Mitral and Aortic Valves*			
1. Annulus alone (mitral)	12/35	8/35	20/36
2. Annulus and leaflets (mitral)	3/3	0/4	3/4
3. Leaflets alone (mitral)	1/2	0/2	2/2
4. Total	16/40	8/41	25/42
Grand Total	28/73	12/73	44/75

*Discrepancies in the number of cases (denominators) are due to incompleteness of records.

Rheumatic Heart Disease.—The above data indicate that calcification of the mitral valve in rheumatic heart disease may involve the annulus, the leaflets, or both; that leaflet calcification is more frequently found in rheumatic than in nonrheumatic hearts; and that about one-half of the 15 rheumatic hearts showed calcification of the aortic in addition to the mitral valve (Table III).

In the present series the average age (at death) of those with rheumatic heart disease and mitral valve calcification was lower, and the average heart weight was more, than in those with nonrheumatic heart disease. The youngest patient with rheumatic heart disease was 16 years of age; there were areas of minimal calcification on the mitral leaflets and aortic cusps; the heart weighed 1,100 grams and was the largest in this series. The average age of 15 rheumatic patients with mitral valve calcification was 47 years, and the average heart weight was 603 grams, while the average age of 59 patients with non-

rheumatic heart disease and mitral valve calcification was 69 years, and the average heart weight was 436 grams.

In rheumatic heart disease the average life span and average heart weight did not differ significantly in patients who had mitral valve calcification alone and in those who had calcification of both the mitral and aortic valves. These varied, however, with the location of calcification on the mitral valve. The average age at death in nine patients with calcification of the ring was 54 years, and in six with calcification of the leaflets only, 34 years. The average weight of the rheumatic heart in the present series was greater in those with leaflet calcification (719 grams) than in those with calcification of the mitral ring (518 grams). Rheumatic heart disease was the most important factor in the development of congestive failure in the entire series.

In cases with mitral valve calcification, generalized arteriosclerosis, hypertension, myocardial infarction, angina pectoris, calcification of the coronary arteries, and renal disease were less commonly associated with rheumatic than with nonrheumatic hearts. None of the patients with rheumatic heart disease and mitral calcification had myocardial infarction or angina pectoris. Only one had generalized arteriosclerosis, and two had hypertension.

Arteriosclerotic and Hypertensive Heart Disease and Generalized Arteriosclerosis.—The annulus fibrosus was the common site of calcification on the mitral valve in patients with generalized arteriosclerosis and in those with arteriosclerotic and hypertensive heart disease (Table III). The 23 cases listed as arteriosclerotic and hypertensive heart disease are included in the group of 35 cases with generalized arteriosclerosis, except for 4 in which there was hypertensive heart disease but no arteriosclerosis. The average life span for these 2 groups was 69 and 70 years, respectively, and the average heart weight was 521 and 461 grams, respectively. These averages were essentially the same in those with aortic in addition to mitral valvular calcification, and were not significantly different in 24 patients without rheumatic heart disease or bacterial endocarditis who had neither generalized arteriosclerosis nor hypertension. Almost all patients with arteriosclerosis or arteriosclerotic and hypertensive heart disease were older than 50 years.

Primary Cause of Death.—The primary cause of death in 78 patients with mitral valve calcification was, in order of frequency: heart disease, carcinoma, and vascular disease, chiefly hypertension. Of the 37 cardiac deaths, one-third of the patients died of rheumatic heart disease, and almost as many died of myocardial infarction. One-fifth of the patients died of arteriosclerotic and hypertensive heart disease, and 4 died of bacterial endocarditis. In only seven of the 23 patients with arteriosclerotic and hypertensive heart disease was death due to the heart; in the remaining 16 cases of heart disease, the cardiac lesion was usually the cause of death. Congestive heart failure was diagnosed in five-sixths of the cases in which heart disease was a primary cause of death; murmurs were usually present in these cases. Angina pectoris was noted in approximately one-fourth of the cases.

DISCUSSION

A new roentgenographic method for ascertaining the presence of mitral valve calcification has been applied to a study of the hearts of 766 unselected patients. This study shows that mitral valve calcification occurred in over 10 per cent of all hearts, and that it was much more common in women than in men. The preponderance of women with mitral valve calcification over men was uninfluenced by the presence of any other associated cardiovascular pathology which we studied. Thus, when aortic valve calcification occurred in combination with mitral valve calcification, as it did in one-half of the cases in this series, the relative frequency of its occurrence in women was nevertheless still much greater than its occurrence in men. The high incidence of women with mitral valve calcification was not due to rheumatic heart disease, which occurred in less than one-fifth of all the cases, particularly since the ratio of the females to males was about the same in this group as in any other division of our cases on the basis of associated pathology. Martens also found the relative incidence of calcification of the mitral ring to be greater among women,[17] and de Oliveira explains this fact by the greater incidence of disturbances in calcium metabolism and of hypertension in women.[20]

In the entire series, calcification was limited to the annulus in 80 per cent of the cases and to the leaflets in 10 per cent of the cases. Although calcification may occur in any inflammatory lesion, it involved the leaflets in less than one-half of the 15 cases of rheumatic heart disease. Moreover, leaflet calcification was found mostly in the young, and involvement of the annulus was found mostly in the aged; these findings are in agreement with those based upon roentgenographic examination of living subjects.[6, 7, 10] Seventy-five per cent of the cases with leaflet calcification occurred in rheumatic heart disease or bacterial endocarditis. The high incidence of associated conditions such as generalized arteriosclerosis (in 50 per cent of the cases), coronary artery calcification (66 per cent), and arteriosclerotic and hypertensive heart disease (33 per cent) suggests that calcification in many of these cases may be noninflammatory in nature. A relation between the degree of calcification and age has been noted.[11] However, Giese[2] and Martens[17] were of the opinion that calcification of the mitral ring and that of the blood vessels were unrelated.

Longevity, the incidence of associated lesions, congestive failure, and heart weight were not influenced by the presence of the additional factor of aortic valve calcification. The largest hearts were those with calcification of the mitral leaflets, and occurred mostly in the younger age groups, in patients with rheumatic heart disease. Clinical x-ray examination of hearts with mitral valve calcification similarly reveals a high incidence of hypertrophy in those with leaflet calcification[6] and similar differences in age and heart size in rheumatic and nonrheumatic heart disease.[6, 10]

Sohval and Gross[12] were of the opinion that calcification in the heart valves does not appreciably alter the prognosis and bears no apparent relation to heart failure or heart disease, but others have suggested that the mitral systolic murmur may be due to mitral insufficiency produced by calcification of the annulus

fibrosus.[19] There is no evidence, from our study, that calcification of the mitral valve, regardless of its location, has an important bearing on clinical heart disease. This conclusion is evident from study of the whole group of 78 hearts with calcification of the mitral valve, but more particularly from study of the 15 hearts with calcification but without associated pathology. This statement applies to cardiac enlargement, murmurs, electrocardiographic abnormalities, heart failure, and cause of death.

Nevertheless, certain facts are of interest and importance. When mitral valve calcification is present, the incidence of associated cardiovascular disease is great; almost one-half of all the patients died of heart disease, usually rheumatic heart disease or myocardial infarction. In hearts showing no cardiac lesion other than valvular calcification, the latter was always limited to the annulus fibrosus. Leaflet calcification is usually regarded as evidence of mitral stenosis or rheumatic heart disease.[10, 18] While this may be true insofar as the clinical demonstration of leaflet calcification is concerned, the more accurate post-mortem method used in this study indicates that only three-fourths of the cases with leaflet calcification had rheumatic heart disease, and that the latter was present in a few cases when calcification was limited to the annulus fibrosus. However, leaflet calcification in rheumatic heart disease indicates a more serious degree of heart involvement than is present when the annulus alone is calcified. These observations are in accord with Epstein's statement that patients with rheumatic heart disease who live past the age of 40 years develop calcium deposits similar in extent and distribution to those of patients with nonrheumatic heart disease[11] but that leaflet calcification indicates an advanced lesion.[10] Others have reported mitral ring calcification in patients with rheumatic heart disease, the youngest of whom was 25 years old.[4, 5] Two-thirds of the 78 hearts with mitral valve calcification had calcification in the coronary arteries; in most of these the valve calcification involved the annulus fibrosus. Epstein also found that disease of the coronary arteries and generalized arteriosclerosis in patients with mitral valve calcification was more frequent in those with nonrheumatic hearts.[11] The clinical application of these facts is impossible without an accurate differentiation between annulus and leaflet calcification.

CONCLUSIONS

1. A new and accurate method for detecting mitral valve calcification reveals that this condition is present in 10 per cent of unselected hearts. It occurs preponderantly in females.

2. Mitral valve calcification, especially of the annulus fibrosus, is in many cases not the result of an inflammatory process.

3. The annulus fibrosus is the most common site of calcification, and this type of deposit is usually found in the aged. The leaflets are involved much less commonly, and then largely in younger age groups; in these patients rheumatic heart disease is frequently present. Calcification may be confined to the annulus in rheumatic heart disease, but this type of deposit is found, as a rule, in a more advanced age group than that in which leaflet calcification is present.

The average heart weight is less in those with annulus than in those with leaflet calcification.

4. Mitral valve calcification does not give rise to symptoms or signs of heart disease. Its clinical importance lies in the fact that it is often an indication of the presence of significant cardiovascular disease.

5. Calcification of the mitral valve is always limited to the annulus fibrosus in hearts showing no cardiac lesion other than the valvular calcification.

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STUDIES ON THE PATHOGENESIS OF PULMONARY EDEMA FOLLOWING BILATERAL VAGOTOMY

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THE changes following bilateral cervical vagotomy have interested investigators for almost two thousand years. The procedure was apparently performed first by the Greek physician Rufus of Ephesus, who lived in the first century after Christ, and a few decades later by Galen. With the revival of science in the sixteenth century, interest in bilateral vagotomy was revised, and during the following centuries this procedure was performed by many experimenters, Valsalva[1] and Morgagni[2] being among the earlier ones. Valsalva was the first to describe pulmonary changes following bilateral vagotomy. These changes were then more thoroughly described by the French clinicians[3] (Vieussens and Sénac), who called the process "inflammation." Since then the interest in this procedure has centered around the changes in the lungs. An important advance was made by Legallois,[4] who was the first to consider laryngeal paralysis and paralysis of the pulmonary vagal fibers as possible pathogenetic factors responsible for pulmonary transudation and consolidation following bilateral vagotomy. The publication of Legallois' work was followed by a lively interest in bilateral vagotomy, which persisted for the greater part of the nineteenth century. The main problem of the studies was the pathogenesis of the pulmonary lesions. This interest stayed alive during the twentieth century and has even increased during the past few years.

Although some of the experiments of these investigators were done on dogs, cats, and guinea pigs, and more recently on rats, most of them were done on the rabbit, and the most important conclusions were drawn from work on this animal. Whenever more than one species of animals was used, the essential findings in the various species were similar in the hands of the same investigator, provided that animals of comparable age were used. Contradictory results, however, were often obtained by the various experimenters, which at times gave rise to sharp polemics, as between Traube and Schiff.

In reviewing the work of previous investigators it may be helpful to have clearly before our eyes the various structures, the functions of which might be disturbed by bilateral vagotomy.

On theoretical grounds the following possibilities emerge: (1) *Airways,* resulting in (a) inspiratory laryngospasm, causing a marked increase in the negativity of the intra-alveolar pressure; (b) inability of the vocal cords to close during deglutition, causing the aspiration of food particles into the airways; (c) loss of sensibility of the tracheal and

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bronchial mucosa, causing the accumulation of mucus and possibly of aspirated food particles in the respiratory tract; (d) paralysis of the bronchial musculature, causing narrowing or even collapse of the flaccid bronchioles during inspiration; and (e) loss of the Hering-Breuer reflex, causing an increase in the negativity of the intra-alveolar pressure as a result of the increased volume of inspired air. (2) *Pulmonary vessels,* resulting in (a) loss of vasoconstrictor tonus, causing dilatation of the pulmonary vessels; and (b) increased capillary permeability, causing transudation into the alveoli. (3) *Heart,* resulting in tachycardia and failure of the heart to adjust to circulatory changes. (4) *Gastrointestinal tract,* resulting in (a) faulty deglutition, and (b) regurgitation of food. Both (a) and (b) lead to the aspiration of food particles.

Most of these factors, singly or in combination, have been considered by previous investigators as the causes of the pulmonary changes following bilateral vagotomy.

Summarizing the conclusions given in the literature of the nineteenth century one may say that there were two main schools of thought. The first considered the pulmonary lesions, i.e., pulmonary edema and pulmonary consolidation, to be secondary to various disturbances of laryngeal, esophageal, or cardiac function, while the second regarded them as a primary disturbance of the function of the pulmonary vessels.

No attempt will be made to give a complete review of the literature on bilateral vagotomy. Only the works that appear to have some bearing on the pathogenesis of pulmonary edema will be reviewed.

The foremost representative of the school of thought which attributed the changes in the lungs to extrapulmonary causes was Traube,[5] who published his first paper on bilateral vagotomy in 1846. He was, apparently, the most original of all his contemporaries, who to a great extent repeated his experiments with some variations.

Traube's most important contributions to the problem were the following: (1) Seven bilaterally vagotomized rabbits in whom tracheotomies had been performed lived for approximately twenty-four hours and showed either no or minimal pulmonary changes at autopsy. (2) In nine bilaterally vagotomized rabbits he tied the esophagus in the neck, cut it above the ligature and assured free drainage of mucus and saliva from the proximal end, thereby preventing the dripping of these substances into the lower airways. None of these animals showed pulmonary edema or consolidation when killed twenty-one to thirty-five hours postoperatively. (3) In four experiments he proved that squamous epithelium from the mouth or pharynx was present in the bronchi and alveoli of vagotomized rabbits killed several hours after the procedure. (4) He collected the secretions from the proximal end of the esophagi of vagotomized rabbits and injected them through a tracheotomy tube into the airways of two healthy rabbits. These died after eight and sixteen hours, respectively, and showed pulmonary edema and consolidation at autopsy. Traube concluded from (1) that the pulmonary changes were not due to the paralysis of pulmonary vagal fibers, from (2) that they were not due to the narrowing of the vocal cords following paralysis of the recurrent nerves, and from (3) and (4) that the pulmonary lesions were due to the failure of the vocal cords to close during deglutition in vagotomized animals, thus allowing mucus from the pharynx to get into the airways and cause aspiration pneumonia.

Traube's chief opponent was Schiff,[6] who concluded that the lung changes were due to pulmonary vasomotor paralysis, for these main reasons: (1) In vagotomized and tracheotomized rabbits, guinea pigs, and dogs, he found pulmonary congestion, edema, and consolidation. He obtained this result at first with his own technique of using a quill or a thin glass tube for a tracheal cannula, but later he confirmed his own results, even when he used Traube's special cannula. This was a cannula into which the lower portion of the trachea was fitted. It also had a shield at its upper end to prevent the dripping of secretions into the bronchi. However, not all of Schiff's animals showed extensive pulmonary changes.

In some of his rabbits and dogs he found only a few small areas of consolidation; otherwise the lungs were normal. It is difficult to judge how often he found such small changes in his animals, as he very cautiously mentions them as: "... diese freilich exceptionellen, aber nicht so sehr seltenen Faelle..." (2) He found widespread pulmonary changes in animals with their esophagi tied and cut. (3) In rabbits he cut the gray portions of the vagal ganglia ("plexus ganglioformis"), leaving the white portions which carry the laryngeal fibers intact, and found the usual widespread pulmonary changes. Frey,[10] however, repeated this experiment and found normal lungs in one rabbit, killed after twenty-two hours. In another, killed after twenty-six hours, very little pulmonary edema and one small area of consolidation were found. This investigator also quotes Friedlaender as having done this experiment on one rabbit, with negative results. (4) Cutting one vagus produces pulmonary changes. By anastomoses between the vagal fibers of the two lungs, or by a hypothetical pulmonary sympathetic innervation, Schiff tried to account for the fact that these changes were of slight degree. Frey, repeating these experiments, found no or minimal pulmonary changes if the rabbits were killed after a few days. If they were allowed to die spontaneously (survival time, two days to four weeks) they showed hyperemia of the lungs which was more marked on the vagotomized side.

Schiff's theory attracted few followers. We are aware of only two in the nineteenth century: Genzmer,[7] whose conclusions entirely coincided with those of Schiff,[6] and Wundt,[8] who assumed that pulmonary vasomotor paralysis was one of the factors producing the changes in the respiratory tract of vagotomized animals.

Billroth[9] using both Traube's and Schiff's methods of tracheotomy, found in his early experiments that the procedure in each case might or might not be followed by pulmonary changes. Later, however, with more careful technique, he never found lung lesions when he used Traube's methods. He also cut the vagi in two pigeons and one duck, because he could demonstrate that in birds only the lower portion of the larynx was supplied by the recurrent nerve. At death all birds showed perfectly normal respiratory tracts. He concluded that the pulmonary lesion following bilateral vagotomy was an aspiration pneumonia due to laryngeal paralysis.

Frey,[10] in his monograph, thoroughly reviewed the literature on bilateral vagotomy and repeated most of the important experiments of previous investigators. His results were quite similar to those of Traube. Using the latter's tracheal cannula, he found pulmonary congestion in his vagotomized rabbits, but in only one a small amount of edema. In rabbits tracheotomized with Schiff's technique he reported marked pulmonary edema and congestion. He also showed that a tracheal cannula may produce pulmonary congestion in nonvagotomized rabbits, and in some of them may even produce edema. Furthermore, he confirmed Traube's findings that cutting of the recurrent nerves in the rabbit produced the same changes as vagotomy, only much more slowly. However, when, in addition to cutting the recurrent nerves the esophagus was tied, thereby favoring the flow of secretions into the trachea, the pulmonary changes appeared as rapidly as in vagotomized animals. Frey thus came to the same conclusions about the pathogenesis of the pulmonary lesions as Traube had.

The other investigators of this period concluded, as Traube had, that the pulmonary lesions were not due to paralysis of the pulmonary vasomotor fibers, but not all of them agreed with him as to the actual underlying cause of the lesions.

Mendelssohn,[11] prior to all these investigators, had come to the conclusion that the lesions in the respiratory tract of vagotomized animals were due to laryngeal paralysis. He advanced the interesting hypothesis that laryngeal paralysis resulted in deficient entrance of air into the lung and consequent suction on the blood vessel. "Sie (i.e., the air) verhält sich zur Schleimhaut der Lunge, wie die Luft unter einem trochenen Schröpfkopf (suction cup)."

All of Mendelssohn's contemporaries agreed that the narrowing of the vocal slit, particularly during inspiration, is not a factor in producing the changes in the lung. This belief was based on experiments of various investigators showing that after artificial constriction of the trachea by a band the lungs were fund to be normal. In order to demonstrate that mucus in the bronchi did not create respiratory obstruction, Traube placed paper

balls in the bronchi. This procedure produced atelectasis, but not pulmonary edema or consolidation.

Claude Bernard[12] came to the conclusion that the pulmonary lesions were produced by the change in the mechanics of respiration which follows bilateral vagotomy, i.e., by the infrequent respirations, with unusually large volumes of tidal air. Long before Bernard, the Englishman John Reid,[13] and, later, Arnsperger[14] and Boddaert,[15] came to similar conclusions. They believed that the unusually deep and infrequent respirations of vagotomized animals caused stasis in the pulmonary capillaries and consequent transudation into the alveoli.

In summary, one may say that the investigators of the nineteenth century by their ingenious experiments greatly contributed to the elucidation of the factors causing the pulmonary changes in vagotomized animals. The fact that they did not distinguish clearly between pulmonary edema on the one hand and pneumonia on the other hand somewhat limits the value of their work from our viewpoint. However, the evidence presented by the bulk of the work, and particularly by the best-controlled experiments, those of Traube, Billroth, and Frey, suggests that all pulmonary changes which follow bilateral vagotomy may be due to a primary disturbance in laryngeal function.

The differentiation between pneumonia and pulmonary edema became distinct in the twentieth century. Kraus,[16] and later Brunn,[17] reported the production of pulmonary edema by the intravenous infusion of large amounts of normal saline into vagotomized animals. Kraus, working on rabbits and cats, thought that this type of pulmonary edema might be due to the loss of innervation of the pulmonary blood vessels. Brunn found that morphine, dial, paraldehyde, and extract from the posterior pituitary did not prevent pulmonary edema in vagotomized rabbits given large amounts of 1 per cent saline intravenously. He observed edema of the glottis in some of his animals and could indeed protect a number, but not all, of his rabbits by tracheotomy.

In recent years, the theory of pulmonary vasomotor paralysis has been supported by the work of Weiser and of Farber.

Weiser[18] believed that vagotomy caused increased permeability of the pulmonary capillaries because in unilaterally vagotomized rats certain dyes (methylene blue, indigo carmine, etc.) introduced into the trachea after death diffused more readily from the lung which had been deprived of its vagal innervation than from the control lung. The amount of diffusion of the dyes was judged by the free eye. Colorimetric determinations were not made on account of small contaminations of the samples with blood.

Farber[19, 20] has investigated the pathogenesis of pulmonary edema following bilateral cervical vagotomy in rabbits and guinea pigs. In rabbits[19] he obtained results in agreement with those of Schiff and others, in that tracheotomized animals showed the same degree of pulmonary congestion and edema as nontracheotomized animals. The main difference was that no evidence of aspiration of food or of secretions from the mouth, nor of bronchopneumonia, was present in the rabbits. In vagotomized guinea pigs[19] under artificial respiration, he observed, after raising the sternum, that the heart beat regularly and vigorously until a few minutes before death, when dilatation of the right side became apparent. Autopsy revealed severe pulmonary edema and conges-

tion. From the fact that the heart action appeared undisturbed on inspection, he concluded that there were no important alterations in the heart which might have caused the pulmonary edema following bilateral vagotomy. In the same paper he reported a series of experiments in which pieces of cotton saturated with 1 per cent novocain solution were placed anteriorly and posteriorly over the lung hila of nonvagotomized guinea pigs under artificial respiration. Severe pulmonary edema and congestion developed just as in vagotomized animals. The type of respiration preceding the onset of pulmonary edema was not described. In a later communication Farber[20] reported the intravenous infusion of large amounts of normal saline, ranging from 135 to 350 c.c., into 20 vagotomized rabbits within ten to fifteen minutes. Ten of these animals were tracheotomized and ten were not. Some of the rabbits died spontaneously soon after the infusion was stopped. The others were killed fifteen minutes afterward. All showed marked pulmonary edema and congestion. There were no important differences noted at autopsy between animals with and those without tracheotomy tubes. The same results were obtained if vagotomy was preceded by a large saline infusion and followed by a small one. Infusion of similar amounts of saline into healthy rabbits produced moderate pulmonary congestion but no edema. The clinical course of these rabbits was characterized by rapid shallow breathing, interrupted only rarely by very short attacks of "respiratory distress" accompanied by generalized convulsions. The vagotomized animals, breathing slowly and deeply, showed similar but more frequent crises, usually commencing one to two minutes after the infusion had been started. Farber was unable to produce pulmonary edema in atropinized rabbits to whom similar amounts of physiologic solution of sodium chloride were given intravenously. He concluded from his first two studies that "neuropathic pulmonary edema," as he termed it, following bilateral vagotomy, was caused by "disturbance to or abolition of the pulmonary vasomotor nerves." In his third paper he suggested that alterations in the pulmonary vessels secondary to loss of vagal innervations were of primary importance in the production of this type of pulmonary edema, but that other processes also were responsible. His evidence suggested to him that pulmonary edema in patients suffering from central nervous system disorders with involvement of the brain stem were caused by disturbances, either central or peripheral, in the vasomotor control of the pulmonary vessels.

Lorber,[21] in contradistinction to the last-named investigators, came to the conclusion that pulmonary edema in vagotomized animals was caused by extrapulmonary causes. He reported that vagotomized rats die within two hours and that the lungs of these animals show extensive pulmonary congestion and edema. He thus confirmed the report of Weiser, whose rats died in three to six hours. Tracheotomy considerably prolonged the life of vagotomized rats, the lungs exhibiting only minimal changes. Lorber thought that "the common denominator in all cases in which pulmonary congestion and edema were seen in any degree was respiratory obstruction." Intrathoracic vagotomy below the recurrent laryngeal nerve on one side, and cervical vagotomy on the other side, performed ten to fourteen days later, permits "almost indefinite survival

(guinea pig and rabbit), unless laryngeal paralysis from the unilateral denervation produces respiratory obstruction (rat, guinea pig and rabbit)." He concluded that pulmonary edema following bilateral vagotomy probably resulted from respiratory obstruction and that circulatory failure might also be a factor of some importance.

Very recently, Short[22] has repeated the experiments on vagotomized rabbits with and without tracheotomy. Under the latter condition, he obtained severe pulmonary edema with regularity, while under the former, moderate pulmonary edema occurred in only three of twelve rabbits. He also showed that a tracheal cannula may produce severe pulmonary edema in nonvagotomized rabbits. Short thought that the appearance of the lungs at autopsy was strongly suggestive of asphyxia, and therefore he concluded that this was the major factor causing the pulmonary changes. In tracheotomized animals he attributed the asphyxia to the presence of mucus plugs. The theory that slow asphyxia was responsible for the pulmonary lesions in vagotomized animals had been first advanced by Schafer.[23]

The interest in bilateral vagotomy has been stimulated in recent years mainly by the occurrence of pulmonary edema in patients with lesions of the central nervous system. Farber's work has been regarded by Luisada[24] as contributing to the evidence that pulmonary edema may be produced by nervous factors. The present study was undertaken mainly to test the validity of this conclusion.

BILATERAL CERVICAL VAGOTOMY AND SYMPATHOTOMY IN THE RAT UNDER ETHER ANESTHESIA

Methods.—Twenty-five young adult rats of piebald strain (*Mus norvegicus*), weighing 150 to 250 grams, were used. Under ether anesthesia the vagus nerve was resected low in the neck. In eight of the 25 rats the sympathetic chains were also cut low in the neck. The clinical course of the animals was observed, with frequent notations of the character of the respirations. If the rats survived, they were also watched at intervals during the first and second nights.

Laryngoscopy was performed in most animals immediately following vagotomy, and in a few cases later during the course. Laryngoscopy was carried out by using as the source of light an ophthalmoscope from which the head piece carrying the lenses had been removed. With the anesthetized animal tied down on its back, the tongue was seized with a blunt forceps and pulled upward. When the light was placed near the posterior portion of the palate, the larynx and the movements of the vocal cords were clearly seen. If death was not observed, the survival time was set arbitrarily at the midpoint between the time the animal had last been seen alive and the time when it was found dead. Complete autopsy was carried out at once if the death of the animal was observed. In some rats, however, post-mortem examination was not performed until one to two hours after death, and occasionally not until several hours thereafter in animals which survived for a long time. The right lung was immediately immersed in 10 per cent formalin. The left lung was placed, without loss of blood or edema fluid, into a weighing bottle. After weighing on an analytic scale, this lung was dried

by exposure to a temperature of 100 to 110° C. until a constant weight was obtained. The water content of the lung was thus determined. In all rats in this series the division or the integrity of the sympathetic chains was checked by dissection under the dissecting microscope.

Results.—Immediately after cutting the second of the vagi the respirations became slow and deep. The respiratory rate varied from 16 to 30 per minute in the great majority of cases, but in a few rats it was as high as 40 per minute. In many animals, but not in all, a marked inspiratory crow appeared immediately or approximately one minute after bilateral vagotomy. Whenever this was present inspirations were quite labored, all auxiliary respiratory muscles being used vigorously. Laryngoscopy of these animals revealed the vocal cords immobile and rather near to the midline but leaving a fair-sized slit open for the passage of air during most of the respiratory cycle. During the second half of inspiration, however, the vocal cords were drawn closely together; the air forced through this narrow pathway produced the respiratory crow.

It is of considerable importance that we observed several rats which did not develop this inspiratory crow but did have labored inspirations immediately after vagotomy. If these animals were not much disturbed by laryngoscopy and did not develop an inspiratory stridor during the procedure, they did not show the inspiratory spasm of the vocal cords.

There was no important difference in the clinical course or survival time, or in the incidence of pulmonary edema between the 17 animals which had only the vagi cut, and the eight which had the sympathetics in addition to the vagi cut (Table I). Hence, the 25 rats will be discussed together. Twenty of these 25 rats could be placed into two groups, which differed in their survival time, clinical course, and also in the pulmonary findings at post-mortem examination.

TABLE I. COMPARISON OF THE EFFECT OF BILATERAL VAGOTOMY AND SYMPATHOTOMY UNDER ETHER ANESTHESIA

	NUMBER OF ANIMALS	SURVIVAL TIME IN HOURS			PULMONARY EDEMA*	
		MINIMUM	MAXIMUM	AVERAGE	NO.	%
Bilateral vagotomy	17	¾	72	19	11	65
Bilateral vagotomy and bilateral sympathotomy	8	2½	88	22	4	50

*Pulmonary edema of moderate or marked degree.

Group With Short Survival Time: The animals in the first group (13 rats) had either continuous or frequently recurrent inspiratory obstruction, to which they succumbed at various intervals ranging from forty-five minutes to fourteen hours. In this group death occurred under extreme inspiratory distress, the rat leaping wildly through the cage in vain attempts at inspiration.

At autopsy these animals showed pulmonary edema of moderate or marked degree. Whitish froth was seen on the cut surface of the right lung and in the bronchi, and in the more severe cases also in the trachea. It also appeared at the hilus of the left lung, which was dropped uncut into a weighing bottle.

At times thin serous fluid was found in the airways. The lungs were usually dark red in color and rather voluminous; if the edema was less marked, they were medium red or mottled and their volume was only slightly increased. In pharynx, larynx, and trachea we observed variable amounts of viscid mucus.

Group With Long Survival Time: The second group (seven rats) also had repeated attacks of inspiratory obstruction, but after these ceased (usually after several hours) the animals breathed quietly, inspiration being only slightly or not at all labored. A slight inspiratory noise was present at times, but periods of inspiratory crowing were observed only rarely. The survival time of these animals ranged from twenty-five to eighty-eight hours. The later course of these rats was characterized by slowly increasing drowsiness and weakness. If aroused, however, the animals were very irritable; if taken out of the cage, they usually developed a transient inspiratory crow. From the mouth and nostrils there often dripped a considerable amount of foul-smelling mucus, which the animals could be observed to chew and swallow. The respiratory rate increased somewhat in the later stages; the rate usually ranged between 40 and 60 per minute. In the rare cases in which these animals were observed at death, the respirations were seen to become more and more shallow and finally to stop. Only one rat, which survived twenty-five hours, was observed to die with signs of inspiratory distress. We have never observed a vagotomized rat to consume solid food. The amount of water they drink is very small.

At autopsy these rats showed either no pulmonary edema or pulmonary edema of such slight degree that it could not be considered as even a major contributing cause of death. The lungs were normal or slightly increased in size, their color was medium to dark red, often mottled, and they showed varying degrees of bronchopneumonia and at times also patchy atelectasis. In this group large amounts of mucus also were found in the airways. The liver showed a moderate degree of congestion at times. No other significant changes were found in either group. The upper row in Table II illustrates the fact that the longer was the survival time of the animals, the lesser was the degree of pulmonary edema.

The water content of the left lung as determined by the dry weight almost invariably paralleled the degree of edema found on gross examination. Occasional disagreement between the two observations might be due to uneven distribution of pulmonary edema in the two lungs, a condition which was observed at times on gross examination of the lungs, or to the presence of interstitial edema not detected on gross examination. The average dry weight of the left lung in the group with pulmonary edema of moderate or marked degree was

TABLE II. RELATION OF SURVIVAL TIME TO DEGREE OF PULMONARY EDEMA (VAGOTOMY UNDER ETHER AND UNDER URETHANE ANESTHESIA)

	DEGREE OF PULMONARY EDEMA			
	MARKED	MODERATE	SLIGHT OR MINIMAL	NONE
Ether anesthesia Average survival time in hours	8.5	9.5	22.5	51.5
Urethane anesthesia Average survival time in hours	19		70	

14.8 per cent; the individual values ranged from 10.5 per cent to 17.5 per cent, except for one instance in which it was 19.7 per cent. In the group without pulmonary edema or with pulmonary edema of slight degree, the average dry weight was 22.9 per cent; the individual values ranged from 22.1 per cent to 26.2 per cent, with one exception of 18.7 per cent.

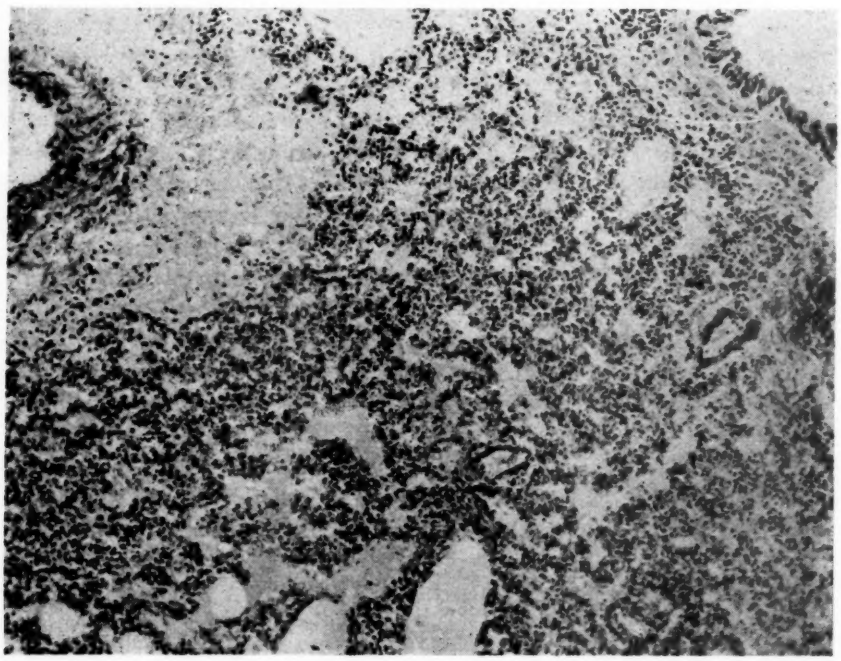

Fig. 1.—Section through lung showing dilatation of the capillaries, and pinkish staining material in some of the alveoli and around the small vein in the left upper corner. In this area there is also extravasation of red blood cells.

The microscopic findings in the lungs usually confirmed the observations made on gross examination, the only exception being our inability to demonstrate small and sometimes even moderate amounts of pulmonary edema under the microscope. The fixation of edema fluid in slices of rats' lungs, which by necessity are thin, was not appreciably improved by dropping the tissue into warmed formalin. In the majority of cases, however, pinkish staining fluid with entrapped air bubbles was seen in the alveoli. The same material was often seen to accumulate around small pulmonary blood vessels, apparently distending the perivascular lymphatics (Fig. 1). At times small areas of emphysema, undetected on gross examination, were seen.

The five rats not included in the previous account because they did not show a similar correlation between survival time and autopsy findings, died after 28, 28½, 12, 10, and 6 hours, respectively. The first two, which were not observed at death, showed moderate and marked pulmonary edema, respectively, but the latter three showed no or minimal edema.

The incidence of pulmonary edema of moderate or marked degree in the entire group of twenty-five rats was 60 per cent (15 rats), which is a surprisingly

low figure in view of the fact that an incidence of 100 per cent has been reported in vagotomized rats. To investigate the possibility that the use of either anesthesia might have influenced our results, the following group of rats was operated upon under a different anesthetic.

BILATERAL CERVICAL VAGOTOMY UNDER URETHANE ANESTHESIA

The methods employed in this series of experiments were the same as in the previous one, except that urethane was used as the only anesthetic and the sympathetics were not cut. Urethane was chosen on account of its negligible effect on circulation and respiration. It was administered to 12 rats by intraperitoneal injection, in amounts varying from 700 to 1,300 mg. per kilogram of body weight. The animals which had received the smaller doses were usually well awake several hours postoperatively. The few rats requiring the larger doses often remained under rather deep anesthesia for longer periods, at times for twenty-four to thirty-six hours.

In this series, in contrast to the previous one, audible and visible inspiratory laryngeal obstruction was rare. Laryngoscopy revealed a vocal slit which was fairly narrow during inspiration and expiration, but only very rarely was there an inspiratory laryngospasm. Nevertheless, inspiration was often, but not always, rather labored immediately after vagotomy. This usually subsided after a variable time, but periods of moderately labored inspiration often reappeared during the later course. The survival time in this group was considerably longer than that in the rats operated upon under ether anesthesia; the average time for the entire group was approximately fifty-three hours, with a range from approximately four and one-half to one hundred six hours.

The autopsy findings differed in two important respects from those of the previous series. First, the incidence of pulmonary edema of moderate or marked degree was considerably lower; and second, the incidence and the extent of bronchopneumonia was much increased, as was also the amount of mucus in the airways. Only four rats of the 12 showed pulmonary edema of a significant degree, while the others had either no or minimal to slight pulmonary edema. Of the four animals exhibiting moderate or marked edema, one had continuous inspiratory laryngeal obstruction for its entire survival time of four and one-half hours, and one suddenly developed severe inspiratory obstruction, leading to death in a few minutes. The other two animals, like most rats in the entire group, had episodes of moderately labored inspiration; they were not observed at death. Again in this series the survival time of the rats developing pulmonary edema of significant degree was much shorter than that of the animals without or with little pulmonary edema (Table II).

The dry weight of the left lung was determined in the majority of the animals in this group. Again there was a close correlation between the amount of pulmonary edema observed on gross examination and the moisture content of the lung.*

This series of rats again showed the importance of respiratory obstruction in the development of pulmonary edema. The following group of experiments was done in an attempt to avoid inspiratory obstruction.

*For this reason the dry weight determination of the lung tissue was omitted in the remaining series of experiments.

RIGHT THORACIC AND LEFT CERVICAL VAGOTOMY

To rule out the factor of laryngospasm, the right thoracic vagus was cut below the origin of the recurrent nerve in a group of six rats, while the left vagus was cut low in the neck immediately afterward. This type of operation, first performed by Genzmer,[7] has recently been performed by Lorber,[21] who, however, cut the left cervical vagus ten to fourteen days after the right thoracic vagus was cut.

Under ether anesthesia, the right sternoclavicular joint was severed and the clavicle reflected laterally, as described by Lorber.[21] The medial portion of the first rib was resected and the second rib was retracted downward. Care was taken not to handle the vagus above the origin of the recurrent laryngeal nerve, below which the vagus was then cut. Left cervical vagotomy followed immediately afterward. The integrity of the right recurrent laryngeal nerve was checked by laryngoscoscopy, which revealed the left vocal cord immobile near the midline, while the right showed the normal vigorous excursions with respiration. At autopsy the right recurrent laryngeal branch was found intact in all cases.

Immediately after, or very shortly after vagotomy, respirations became slow and deep, inspiration being moderately labored in spite of the absence of laryngospasm. This type of respiration continued for some time, usually not more than twelve hours, and then gave way to somewhat faster, less deep, and little or not at all labored breathing. Periods of moderately labored inspiration recurred later during the course; these could be eased temporarily by wiping thick mucus out of the hypopharynx. As to their general behavior, these rats were quite similar to those with bilateral cervical vagotomy. The average survival time in this group was sixty-six hours, varying in individual rats from thirty to one hundred twenty hours. At post-mortem examination pulmonary edema of moderate or marked degree was found in three rats; two rats showed no pulmonary edema and one showed very slight pulmonary edema. The lungs of all animals were moderately congested and showed varying degrees of bronchopneumonia.

As has been demonstrated, inspiratory obstruction was not avoided by the operative procedure described. Therefore, at least in the rat, thoracic vagotomy is not a suitable procedure for ruling out the obstructive factor associated with bilateral vagotomy.

The question arises, of course, whether respiratory obstruction, and particularly inspiratory obstruction, can actually produce pulmonary edema. The investigators of the nineteenth century, with the exception of Mendelssohn,[11] denied this. They based their conclusion on experiments in which respiratory obstruction was produced by narrowing the trachea with a constricting band or by letting the animal breathe through a very narrow cannula. These procedures failed to produce pulmonary edema or consolidation. Traube[5] also obstructed bronchi by paper balls, and consequently found atelectasis but not the pulmonary changes produced by vagotomy. It should be noted that all these procedures gave rise to inspiratory *and* expiratory obstruction. They, therefore, do not simulate the condition present in the nontracheotomized animal with bilateral

vagotomy, and possibly not even that in the tracheotomized animal, as we shall point out later.

In recent years the statement has been made that inspiratory obstruction alone may produce pulmonary edema. There is, however, little experimental evidence reported in detail to substantiate this statement. Warren, Peterson, and Drinker[25] demonstrated markedly increased lymph flow from the lungs in dogs breathing against inspiratory resistance. Moore and Binger[26] found pulmonary edema in only one of six dogs breathing against inspiratory resistance. The other animals showed mild to moderate pulmonary congestion, which usually was more marked over the lower portions of the lungs. Barach[27] reported that "edema of the lungs may occur in three hours, with circulatory failure, after continuous breathing through a resistance." In another paper[28] he mentions that dogs inspiring against a negative pressure of 4 cm. of water for six hours show a progressive rise in the intrapleural negative pressure and that at autopsy severe pulmonary congestion and edema of the hilus and basal regions, with emphysema at the periphery, were found.

The following experiments were carried out to determine whether well-marked pulmonary edema could be produced with regularity by causing rats to breathe against inspiratory resistance and whether expiratory resistance in addition would change the incidence of pulmonary edema.

RATS BREATHING AGAINST INSPIRATORY RESISTANCE

Methods.—Rats of the same strain and of approximately the same weight as those in the previous series were used. Under intraperitoneal urethane anesthesia a Y-shaped tracheal cannula of thin metal was inserted. Each of its arms was connected by rubber tubing to a somewhat modified Marriotte tube (Fig. 2). As illustrated, the tubes offer no resistance to inspiration or expiration. By immersing the glass tube touching the water surface in *A* more or less deeply into the water, any desired degree of inspiratory resistance can be produced. Similarly various degrees of expiratory resistance are produced by lowering the corresponding glass tube in *B*. After insertion of the tracheal cannula, no inspiratory resistance was introduced for fifteen to forty-five minutes. This was a control period to demonstrate proper operation of the cannula without obstruction. Then inspiratory resistance, usually measuring 4 to 5 cm. of water, but at times measuring up to 8.5 cm. of water, was produced, according to what resistance the particular animal could overcome. If the resistance was too high, no air bubbles were sucked through the water in tube *A*, and consequently rebreathing and marked anoxemia would have occurred had the resistance not been reduced. During the later course a reduction of the inspiratory resistance to 2.5 cm., or even to zero, was necessary for short periods of time to prevent asphyxia and premature death of the animals. The rats were observed very closely and changes in respiration were noted. Complete autopsy was performed either immediately after or shortly after death. A few representative lung specimens were examined microscopically.

Results.—In a few preliminary experiments, the animals survived only two to three hours. At autopsy they showed considerable congestion of the lungs,

but no pulmonary edema. Consequently, an effort was made to keep the rats alive for longer periods of time. Of 10 consecutive animals, nine lived from approximately three to six hours under inspiratory resistance varying between the limits outlined previously. One animal survived for only one and one-half hours. The average survival time of the ten rats was approximately four hours. The character of the respiration under inspiratory resistance was as follows: The respiratory rate was essentially unchanged, increasing or decreasing not more than 10 to 15 respirations per minute from an initial rate of 100 to 140. This is in accordance with the findings of Anrep and Samaan.[29] Moore and Binger[26] found that dogs under sodium barbital anesthesia, when made to

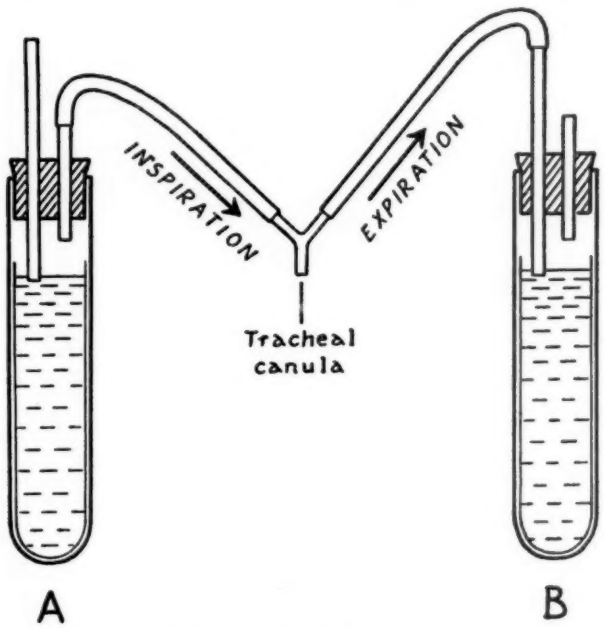

Fig. 2.—Explanation in text.

breathe against inspiratory resistance, developed a considerable increase in the respiratory rate. In our animals, when the resistance was too high to be overcome by the inspiratory effort, a definite slowing of the respirations was noted. The depth of the respirations in our rats was affected only a little by inspiratory resistance, but a slight increase in the depth could usually be detected. Slight to moderate inspiratory retraction of the costal margins was always present. There was slight dilatation of the alae nasi, but none of the other auxiliary respiratory muscles were used. This type of breathing remained unchanged until the terminal period, the onset of which occurred from one-half hour to a few minutes before death. At that time the animal gradually became unable to overcome the inspiratory resistance. Respirations became slow and shallow, rebreathing began, and respirations ceased within one to two minutes, unless the resistance was lowered at once. In some animals, if the resistance was lowered temporarily, to be raised again after a few minutes, life

could be prolonged for periods up to one-half hour. Some animals died during a brief absence of the observer from the laboratory. At autopsy all 10 animals showed pulmonary congestion and pulmonary edema of moderate to marked degree. Peculiarly, edema was always, and congestion was at times, more marked in the left lung than in the right. The color of the lungs of the various rats varied from light red to rather dark red. Pulmonary edema was not necessarily more marked in the dark red than in the light red lung. In the latter there always was one dark red area in the hilar region of the left lung. The rat which survived for only one and one-half hours had the least pulmonary edema. In the other animals, however, the degree of pulmonary edema was not always proportionate to the length of survival. The pulmonary edema seen so readily on gross examination of the lungs could not be seen microscopically in all cases in which sections were obtained. We encountered here the same difficulty in fixing the intra-alveolar transudate as we did in the vagotomized animals. Dilatation of the capillaries was always present and often marked. In addition, small areas of emphysema were noted.

RATS BREATHING AGAINST INSPIRATORY AND EXPIRATORY RESISTANCE

The same methods were used as in the previous experiments except that expiratory resistance was added to the inspiratory resistance. In four rats the expiratory resistance was approximately one-half the inspiratory, while in the other animals it was of equal magnitude.

Results.—In this group the respiratory rate was always reduced, usually by one-fourth to one-third of the initial rate, but in a few animals only by 8 to 12 respirations per minute. This is in agreement with the finding of previous investigators that expiratory resistance diminishes the respiratory rate. Respirations in this series were deeper and more visibly labored than those in the rats breathing against inspiratory obstruction only. One animal in this group survived for approximately one and one-half hours; the survival times of the others ranged from approximately two and one-half to seven hours, the average for the entire group being approximately four hours. Death occurred in a manner similar to that of the preceding series. At autopsy two of the 13 rats in this group showed pulmonary edema of moderate, and two of minimal degree. In the other animals only slight pulmonary congestion was present.

The experiments in the last two groups of rats show that pulmonary edema may be produced with regularity if the animals breathe against inspiratory resistance only.

Farber[20] has raised the important objection that pulmonary edema following vagotomy and intravenous infusions of large amounts of normal saline could not be attributed to inspiratory obstruction, as the edema occurred too rapidly to be due to this factor. To investigate the validity of this objection the following experiments were performed.

RAPID INTRAVENOUS INFUSION OF NORMAL SALINE IN VAGOTOMIZED RATS WITH TRACHEOTOMY AND IN RATS BREATHING AGAINST INSPIRATORY RESISTANCE

Methods.—Rats similar in weight to those in the previous series were used. Under intraperitoneal urethane anesthesia a tracheotomy was performed and

the Y-shaped tracheal cannula connected with the Marriotte tubes in a group of six rats. No respiratory resistance was produced, the glass tubes just touching the water surface. The cervical vagi were cut and immediately afterward the infusion of an 0.85 per cent solution of sodium chloride was started. The solution was administered by drip from a graduate cylinder which was kept at a constant height in all experiments. The cylinder was connected to a glass adapter connected to a 24-gauge hypodermic needle by means of rubber tubing. In all experiments the needle was inserted into the right external jugular vein just above the clavicle, the tip of the needle pointing toward the rat's head. The rate of infusion, varying approximately from 1.5 to 2 c.c. per minute, was kept fairly constant throughout these experiments. There was one exception, in which a smaller quantity of fluid was given. Animals which did not die spontaneously were killed by the intravenous injection of a 0.05 per cent solution of sodium cyanide: respirations stopped after a few seconds, and were usually accompanied by several convulsive movements.

The procedure in the second group of six rats was identical except that no tracheotomy was performed.

In a third group of six tracheotomized but not vagotomized rats, inspiratory resistance of 4 to 7 cm. of water was produced, and then the intravenous infusion was started at a rate similar to that of the previous group.

Results.—In the animals in which vagotomy was performed, respirations became very slow and deep immediately following this procedure. At the same time the prolonged inspiration became somewhat labored, while the relatively short expiration remained perfectly easy. Usually the labored inspiration was accompanied by a moderate increase in the rise of water in the expiratory tube (Fig. 2), thus indicating an increase in the negativity of the intrathoracic pressure. Very soon, as the intravenous infusion was running in, inspirations became more labored, and in some animals continued unchanged until death, while in others they gradually became even more labored. The respiratory rate in some rats either remained essentially unchanged or showed a moderate increase during the later course. In five of the six vagotomized rats 50 to 65 c.c. of saline were given over a period of twenty-seven to forty minutes. These animals were killed by intravenous injection of sodium cyanide a few minutes after ending the infusion. The sixth rat died spontaneously after twenty-four minutes when 22 c.c. of saline had been infused. In this animal and in one other, a very marked degree of pulmonary edema extending up into the trachea was found. The other rats showed pulmonary edema of moderate degree, except for one in which only a small amount of pulmonary edema was present. The lungs of all were moderately or markedly congested.

None of the animals in the second group (vagotomized, but not tracheotomized) showed evidence of laryngospasm. Consequently, inspiration was only slightly labored in the beginning of the experiment, and remained so in some instances up to the end, while in others it became moderately labored during the later course. In this group the amount of intravenous saline and the time in which it was administered were quite similar to those conditions in the tracheotomized group. All rats in the second group were killed a few minutes

after ending the infusion. At autopsy the amount of pulmonary edema was definitely less than that found in the first group. There was never any frothy fluid in bronchi or trachea. The amount of pulmonary edema on the cut surface of the left lung was slight in all cases; in the right lung the edema was slight in four cases, and of moderate degree in two. Pulmonary congestion was slight in four rats and of moderate degree in the remaining two.

The group of six rats breathing against inspiratory resistance and receiving intravenous saline showed respirations very similar to those described above in rats breathing against inspiratory resistance only. Respirations became slow and labored only immediately before death. Until then they continued at a normal rate and were not at all or only slightly labored. Death occurred spontaneously in five animals in periods of from twenty-three to forty-two minutes. The sixth animal was killed by intravenous sodium cyanide thirty-eight minutes after the infusion had been started. The amount of saline injected ranged from 45 to 60 cubic centimeters. At autopsy two rats had marked pulmonary edema extending up into the trachea, three had pulmonary edema of moderate degree and one, of slight degree. The lungs of all showed moderate or marked pulmonary congestion.

PLASMA AND BLOOD VOLUME DETERMINATION IN BILATERALLY VAGOTOMIZED RATS

In an additional group of rats we tried to determine the mode of death of those animals which survived bilateral vagotomy for a considerable time. In this group plasma and blood volume determinations were made in order to investigate the possibility that peripheral circulatory collapse developed in these animals.

Methods.—In healthy rats, weighing from 160 to 240 grams, blood volume determinations were carried out by the method of Gibson and Evans[30] and Gibson and Evelyn[31] as modified by Beckwith and Chanutin[32] for the rat, with only minor modifications adopted by Williams and Barnum.[33] The first blood sample was obtained from the rat's tail ten minutes after injection into the exposed external jugular vein of an accurately measured amount (200 to 300 mg. in various rats) of a 1 per cent solution of T-1824 from a calibrated tuberculin syringe. Four or five additional blood samples were taken subsequently at five-minute intervals. The plasma samples were diluted 60 times with normal saline. The micro attachment of an Evelyn photocolorimeter* was used for the colorimetric readings. Normal saline, rather than diluted plasma, was used as the standard solution, as it has been shown that it gives the same colorimetric reading as highly diluted plasma.

The blood volume determinations were done under urethane anesthesia, supplemented by small amounts of ether when necessary. One rat, BV1, had 1 mg. of sodium pentothal, intraperitoneally, in addition. Immediately after the last blood sample had been taken, bilateral vagotomy was performed. In all but one of the animals the nerve was cut in the cervical region. Rat VTH7 alone was

*The author expresses his thanks to Dr. Maxwell Little of the Department of Physiology and Pharmacology of the Bowman Gray Medical School for helpful advice in setting up this method and for the loan of the Evelyn photocolorimeter.

subjected to a right-sided thoracic vagotomy. It proved very difficult to determine the right moment for the second blood volume determination, as the time of death of vagotomized rats cannot be predicted with any accuracy. Thus many animals died either before or during the second blood volume determination. Out of a group of approximately 22 rats, the second blood volume determination was successfully completed in only 10. It was carried out in these animals twenty-two to twenty-four hours after vagotomy. At this determination, blood was obtained before injection of the dye and the plasma sample, diluted 60 times, served as the standard for the colorimetric readings. The clinical course of the rats in this group was quite similar to that in the urethane series described previously, the only difference being the shorter period of anesthesia, since smaller amounts of urethane (approximately 700 mg. per kilogram of body weight) were given.

TABLE III. BLOOD AND PLASMA VOLUMES BEFORE AND AFTER BILATERAL VAGOTOMY

	PLASMA VOLUME*			BLOOD VOLUME*			
RAT	BEFORE	AFTER	CHANGE† %	BEFORE	AFTER	CHANGE† %	REMARKS
VTH7	3.7	2.7	-27.0	7.1	5.0	-29.6	Only animal with thoracic vagotomy
BV1	3.4	3.6	+ 5.8	7.3	6.8	- 5.9	
BV6	4.8	4.1	-14.6	7.5	6.6	-12.0	
BV7	3.8	3.7	- 2.6	7.4	6.1	-17.6	
BV10	4.1	3.3	-19.5	7.8	6.1	-21.8	Animals transfused
BV11	4.4	3.4	-22.7	7.9	6.0	-24.0	
BV13	3.4	3.7	+ 8.8	-	-	-	
BV19	4.4	3.6	-18.2	8.3	7.7	- 7.2	
BV20	4.7	4.1	-12.6	8.5	8.0	- 5.9	
BV21	3.3	3.2	- 3.1	6.7	6.2	- 7.5	
Total average	4.0	3.5	10.6	7.6	6.5	14.6	

*In cubic centimeter per 100 grams of body weight.
†Values obtained on the basis of preoperative body weight.

Results.—The values for plasma and blood volumes in ten rats before and after bilateral vagotomy are charted in Table III. The plasma volumes of our normal rats ranged from 3.3 to 4.8 c.c. per 100 grams of body weight, with an average of 4 cubic centimeters. The corresponding values for blood volume varied from 6.7 to 8.5 c.c. with an average of 7.6. Following vagotomy the plasma volume was slightly increased in two rats and was decreased in eight. In these eight the amount of decrease ranged from 2.6 to 27 per cent. The greatest decrease (27 per cent) occurred in the animal in which the right thoracic vagus had been cut and which, therefore, had been exposed to much greater operative trauma than the other animals. The change in blood volume did not always run parallel to the change in plasma volume. Of the first four rats in the series one (Rat BV1) showed a decrease of 5.9 per cent in the blood volume, while the plasma volume was increased by 5.9 per cent; and another (Rat BV7) had a decrease of 17.6 per cent in the blood volume, while the plasma volume was decreased by only 2.6 per cent. This discrepancy was attributed to the removal of approximately 1 c.c. of blood during the first blood volume determination. In the remaining six animals in the series, the amount of blood removed was replaced by an equal amount of citrated rat blood immediately after the first blood

volume determination. In these animals there was a rather close agreement of the blood and plasma volume changes, with one exception (Rat BV19), in which the decrease in plasma volume was 11 per cent greater than the decrease in blood volume. The average decrease in plasma volume was 10.6 per cent for the entire group. In only four of the 10 rats was there a reduction of the plasma volume of more than 15 per cent.

Thus, in the majority of our rats peripheral circulatory failure did not appear to be an important factor. We believe that, in the rats not dying of pulmonary edema, bronchopneumonia and inanition were the major causes of death. Our study does not rule out, of course, the possibility of peripheral circulatory collapse later in the course, particularly shortly preceding death.

Plasma and blood volume determinations on five vagotomized rabbits were performed by Farber.[20] In two, an insignificant increase and decrease, respectively, of the plasma volume were present, while the decreases in the other three animals ranged from 17.6 to 30.7 per cent. The blood volumes of the rabbits were more uniformly decreased, but some of his animals had suffered considerable hemorrhage from the trachea. The main difference in the arrangement of his study and ours was that his animals showed clinical evidence of pulmonary edema when the plasma volume determination was performed. The results obtained, however, are not strikingly different. The fact that he obtained significant reductions of the plasma volume in a higher percentage of his animals cannot be evaluated on account of the small number of animals used.

In eight of our rats, which appeared in good enough condition following the second blood volume determination, the mean arterial blood pressure was measured by cannulation of the aorta with a mercury manometer. The readings ranged from 100 to 140 mm. Hg in various animals, thus indicating a normal or slightly elevated arterial pressure.

The heart rate before and after vagotomy was determined in this series by taking electrocardiograms. The heart rate before vagotomy varied from 315 to 500 per minute in various animals. A few minutes after vagotomy it was usually found to be elevated by 100 to 250 beats, but occasionally only by 50 beats, per minute.

The animals surviving the second blood volume determination were killed by withdrawing the cannula from the aorta, which caused death in fifteen to thirty seconds. The two rats in which aortic cannulation was not performed were killed by decapitation. In none of these ten animals was there any pulmonary edema. On the other hand the rats dying spontaneously or during the second blood volume determination showed moderate or marked pulmonary edema in approximately half the cases.

DISCUSSION

Until recently the rat had been used only sporadically as the experimental animal for investigations concerning the effects of bilateral vagotomy. In recent years, however, two important studies have appeared in which the rat was used exclusively (Weiser[18]) or predominantly (Lorber[21]). These two investigators came to totally different conclusions about the pathogenesis of pulmonary edema

following bilateral vagotomy, but agreed in an important finding, namely that all vagotomized rats died within a few hours, autopsy revealing moderate to severe pulmonary edema in all cases. In contrast, many of our rats lived for a considerably longer period, some of them up to three or four days. Moreover, only two-thirds of our animals operated upon under ether anesthesia and only one-third of those operated upon under urethane developed pulmonary edema of moderate or marked degree.

This important discrepancy between our findings and those reported by previous investigators is not due to accidental cutting of the cervical sympathetic chains in addition to the vagal nerves, as rats in which the vagi only and others in which sympathetics and vagi were cut showed similar survival times and a similar incidence of pulmonary edema.* We believe the reason for the discrepancy to be the lesser degree of laryngospasm and, therefore, of inspiratory obstruction in our rats.

That the larger experimental animals, apparently with the exception of the rabbit, may survive bilateral vagotomy practically indefinitely has been shown repeatedly. Schafer[23] demonstrated that bilaterally vagotomized cats could be kept alive for many months if the vocal cords had been cauterized. That dogs can survive in the absence of vagal innervation of the lungs and heart was demonstrated by Boothby and Shamoff,[34] who divided all vagal branches between the recurrent laryngeal nerve and the gastrointestinal branches. Pavlov[35] also reported survival of dogs if one vagus was cut below the recurrent laryngeal nerve and the other in the neck.

Laryngospasm, however, is not the only cause of inspiratory obstruction in vagotomized rats. In rather deeply anesthetized animals laryngospasm may never occur. Furthermore, a few hours after vagotomy the vocal cords assume the cadaveric position, and remain in this position unless the animal is disturbed. Nevertheless, in these groups of animals severe inspiratory obstruction may occur. Undoubtedly, in most instances, this is due to accumulation of mucus in the airways; it can at times be alleviated by wiping out mucus from the hypopharynx. When this is not possible, the point of obstruction may be lower down in the respiratory tract. Mucus was apparently an important factor causing inspiratory obstruction in those rats which had one cervical and one thoracic vagus cut. In spite of the fact that laryngospasm was ruled out in these animals, some of them still showed severe inspiratory distress.

It may be asked why the accumulation of mucus should give rise to obstruction which is predominantly inspiratory. We believe this may be due to the movement of mucus plugs from channels of wider diameter to channels of smaller diameter during the inspiratory effort. Thus, an amount of mucus incapable of creating obstruction higher up will produce obstruction at a point lower in the airways. During the expiratory effort the plug will move in the opposite direction and therefore will be much less likely to produce respiratory obstruction. (That localized expiratory obstruction may nevertheless occur may be

*Cutting of the cervical sympathetics, which probably leaves most pulmonary sympathetic fibers intact, does not, of course, disprove the possibility that thoracic sympathetic denervation might influence the pulmonary changes following bilateral vagotomy.

indicated by small areas of emphysema which were noted on microscopic examination.)

The importance of inspiratory obstruction as the primary factor causing pulmonary edema in vagotomized rats is emphasized by the following points: (1) Bilateral vagotomy in the rat under ether anesthesia does not necessarily produce pulmonary edema. (2) Rats surviving the period in which inspiratory obstruction is marked rarely show pulmonary edema. (3) Urethane anesthesia decreases laryngospasm and further decreases the incidence of pulmonary edema. (4) All rats showing pulmonary edema of significant degree had either marked continuous or marked intermittent labored inspiration for a variable period before death.

Our studies do not support the conclusion of previous investigators (Schiff, Farber) that pulmonary vasodilatation and increased capillary permeability of neuroparalytic origin are important factors in the production of pulmonary edema of this type. Further important proof that pulmonary vascular changes are, at the most, of secondary importance comes from the fact that some of the previous workers (Traube, Frey) regularly prevented the production of significant pulmonary changes by tracheotomizing their animals before vagotomy. Billroth, and even Schiff at times, obtained similar results in some of their animals. Lorber observed that in his tracheotomized vagotomized rats pulmonary edema was produced only if respiratory obstruction occurred through the accumulation of mucus in the tracheal cannula or in the airways. It is true that a few workers found pulmonary edema and congestion even in tracheotomized animals. But the fact that this occurred in the hands of some investigators, while not in the hands of others, seems to indicate that the difference in the results was due to a difference in technique.

The theory that pulmonary vasodilatation is directly due to vagotomy (i.e., to denervation of the pulmonary vessels) also rests on insecure ground, because the importance of pulmonary vasomotor fibers in regulating the blood flow through the lungs is still controversial. While some investigators believe that vasomotor fibers play an important part in this regulation, others deny this. For a discussion of this subject the reader is referred to the writings of Daly,[36] Wiggers,[37] and Hamilton.[38a] The most recent work, that of Hamilton and his co-workers,[38b] who used intact unanesthetized animals and differential manometers, is probably the most convincing investigation of the pressure relationships in the pulmonary circulation up to date. From this work Hamilton reached the conclusion, first expressed by Dixon and Hoyle,[39] that "the vasomotor activity of the pulmonary arterioles is a feeble vestigial mechanism, which is without important function."

The theory of Traube and his school, namely that the inability of the vocal cords to close during deglutition is responsible for the pulmonary changes following bilateral vagotomy, can be accepted only to explain bronchopneumonic lesions, and possibly pulmonary edema of late onset, which is perhaps of inflammatory origin. Early pulmonary edema, particularly that following vagotomy plus intravenous infusion of saline, cannot be explained on this basis.

It also appears doubtful that slow asphyxia, as such, may produce pulmonary edema. This theory was first postulated by Schafer[23] and recently was restated by Short[22] to explain the pulmonary lesions in bilaterally vagotomized animals. According to Drinker's studies,[40] a very marked degree of anoxia has to be present before increased pulmonary transudation, as evidenced by an increase in pulmonary lymph flow, appears. This increase did not take place until the oxygen content of the inspired air was lowered to 8.5 per cent. Drinker thought that even this increase in lymph flow originated only from those areas of the lung which were poorly or not at all aerated on account of the use of artificial respiration. This relative immunity of the lung capillaries to lack of oxygen can probably be explained on the basis that they may derive their oxygen supply not only from the blood but from the alveolar oxygen as well. That severe anoxia exists in vagotomized animals has never been shown. It is unlikely to be a causative factor in the production of pulmonary edema in the short experiments that employ vagotomy plus the intravenous administration of fluids. It may be an additional factor in vagotomized animals with relatively long survival times, but we do not believe that it is of primary importance.

It appears from our studies that a close correlation exists between the occurrence of inspiratory obstruction and the development of pulmonary edema in vagotomized animals. This causal relationship was first suggested by Mendelssohn.[11] Recently Lorber[21] concluded that respiratory obstruction was the most important factor producing pulmonary edema in vagotomized animals.

Our experiments have shown that pulmonary edema of moderate to marked degree can actually be produced with regularity by inspiration against resistance. In rats breathing against inspiratory resistance, or in rats with inspiratory obstruction, a markedly negative intra-alveolar pressure must be present during the forced inspiratory effort. This abnormal negative pressure will tend to overcome the osmotic pressure in the pulmonary capillaries and draw a transudate into the alveoli.

We did not attempt to measure the intrapulmonary pressure in our animals and were unable to measure intrapleural pressure in rats without producing pneumothorax of considerable degree. That the intra-alveolar pressure was highly negative in animals breathing against inspiratory resistance was indicated by the following observations. Under ordinary respiration the water in tubes *A* and *B* (Fig. 2) was sucked up into the glass tubes touching the water surface during inspiration in *B* and during expiration in *A*. *A* and *B* thus acted alternatively as water manometers, giving a rough measurement of the pressure in the other tube and in the respiratory tract. Under normal respiration, with the tubes just touching the water surface, the water rose in them approximately 3 to 4 cm., thus indicating a negative pressure in the respiratory tract during inspiration and a positive pressure during expiration. When inspiratory resistance was produced, the water in the expiratory tube rose to approximately 9 to 12 cm. during inspiration, thus indicating a considerable increase in the negativity of the intrapulmonary pressure. The pressure during expiration

remained virtually unchanged in these experiments. All these animals developed pulmonary edema. If, however, expiratory resistance also was introduced, there developed a considerable increase in positive expiratory pressure as shown by high rises of water in the inspiratory tube. In most of these animals, consequently, pulmonary edema did not develop.

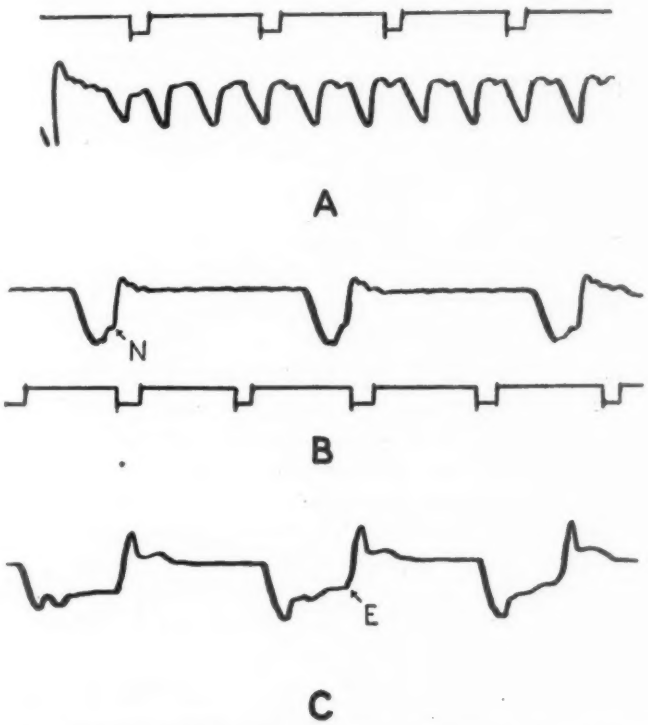

Fig. 3.—*A*, Respiratory tracing before vagotomy (inspiration = downstroke, expiration = upstroke). *B*, Immediately following vagotomy. That inspiration continues up to notch *N* is shown in *C*, in which air withdrawn was pushed back at *E*. Time tracing in seconds.

Similar observations were made in tracheotomized vagotomized animals. In these there was always a higher rise of the water during inspiration than during expiration. The difference was not as striking as in the rats breathing against inspiratory resistance. Usually a difference of 2 to 3 cm. was observed, but occasionally it was as much as 5 to 6 centimeters. This finding strongly suggests that, following vagotomy, there was an increase in the negativity of the intra-alveolar pressure during inspiration.

The objection might be raised that in vagotomized animals with a tracheal cannula there could not have been inspiratory obstruction, since laryngospasm was ruled out in such experiments. We observed, however, that inspiration in these animals was moderately labored and prolonged immediately after vagotomy, that is, at a time when pulmonary congestion and edema, or the accumulation of mucus, could not have been responsible for this type of respiration. We also observed that labored and prolonged inspiration with laryngospasm developed in

rats with the right thoracic and the left cervical vagus cut,* apparently before the accumulation of mucus could take place.

We tried to obtain additional objective evidence to substantiate the observation that inspiration appeared prolonged and labored even in tracheotomized rats with bilateral vagotomy, and that it occurred immediately following vagotomy, before mucus could accumulate in the airways. In three rats, breathing through a Y-shaped tracheal cannula connected to Marriotte tubes, respirations were recorded before and immediately after bilateral vagotomy, on a kymograph from a small tambour, which was connected by a T tube into one of the circuits. Satisfactory records were thus obtained (Fig. 3). The relative duration of inspiration and expiration is very distinct before, but not after, vagotomy. As the volume of respiration increases, overshooting occurs in the tambour during inspiration. That inspiration actually lasts up to the end of the notch *N* (Fig. 3, *B*) was proved by connecting a syringe instead of a rat to the system. When 0.5 c.c. of air was quickly injected, the same overshooting occurred as did the vagotomized rats, the lever then remaining at a lower level until the plunger of the syringe was pulled back (Fig. 3, *C*). The absolute and relative durations of inspiration and expiration in two rats, before and after bilateral vagotomy, are seen in Table IV. In a third rat we obtained similar results, which are not reported in detail since no time tracing was taken. These experiments demonstrated that vagotomy approximately doubled the duration of a single inspiration, while it did not change a single expiration. On account of the slow respiration following vagotomy, the total duration of inspiration was reduced, but the duration of expiration per minute was much more reduced. The increase in the ratio inspiration to expiration, following vagotomy, would probably have been even more striking had not the system through which the rat was breathing in itself offered some resistance to inspiration. The presence of such resistance was indicated by the relative prolongation of inspiration even before vagotomy.

Consequently, we may say that immediately following vagotomy inspiration becomes prolonged and labored, that it is accompanied by an abnormal increase in the negativity of the intra-alveolar pressure, and that this is not counteracted by a prolonged expiration or an increase in the positive pressure during expiration. Again we want to emphasize that these pressure relationships

TABLE IV. DURATION OF INSPIRATION AND EXPIRATION BEFORE AND AFTER BILATERAL VAGOTOMY

		INSPIRATION*		EXPIRATION*		QUOTIENT INSPIRATION
		SINGLE	PER MINUTE	SINGLE	PER MINUTE	EXPIRATION
Rat K2	Before vagotomy	0.21	22.05	0.11	11.55	1.9
	After vagotomy	0.41	13.94	0.10	3.40	4.1
Rat K3	Before	0.17	23.80	0.11	15.40	1.5
	After	0.34	10.88	0.11	3.54	3.1

*Duration in seconds.

*The question whether the labored inspiration was due to a laryngeal reflex was answered by doing a complete laryngectomy in three tracheotomized, vagotomized rats. The clinical course, particularly the type of respiration and the pathologic findings in these animals, which also received intravenous saline, was quite similar to those with intact larynx.

will favor the transudation of fluid into the alveoli. It is clear, however, that these conditions do not necessarily lead to pulmonary edema. In our rats, as we have mentioned before, inspiration often ceased to be labored and prolonged at varying intervals following vagotomy. It was in these animals that pulmonary edema was not found at autopsy.

The phenomenon of labored and prolonged inspiration immediately following vagotomy might be explained by two possible mechanisms: One possibility is that the very slow and deep inspiration of vagotomized animals, which is due to the loss of the Hering-Breuer reflex, as such, induces a marked increase in the negativity of the intra-alveolar pressure on account of the increased inspiratory volume of air. The second possibility, first suggested by Auer and Gates,[41] was that the bronchioles of vagotomized animals may become narrowed during inspiration due to the flabbiness of the bronchial musculature, which has been deprived of its nervous innervation. This phenomenon could, of course, occur only in bronchioles (as they contain no cartilage in their walls) and not in the bronchi. The dilatation of the bronchioles in vagotomized rabbits was clearly demonstrated in Short's microscopic studies.[22] That under abnormal conditions the bronchial lumen may become narrowed during inspiration has been observed by Amberson[42] through the bronchoscope in a patient with chronic nontuberculous fibrosis, emphysema, and pulmonary infection, and in two patients with pulmonary tuberculosis. As Amberson had no direct evidence concerning the underlying pathologic lesion, he assumed that the phenomenon was due to atrophy or malacia of the cartilages.

Either of the two mechanisms, but particularly the latter one, would increase the negativity of the intra-alveolar pressure during inspiration. Thus the same basic mechanism would operate in vagotomized rats, in which laryngospasm is either spontaneously absent or artificially obviated by tracheotomy, as would operate in vagotomized rats with laryngospasm. That there are also other factors favoring the occurrence of pulmonary edema during forced breathing, besides an intra-alveolar pressure of abnormal negativity, is indicated by the work of Hamilton[38a] on anesthetized dogs breathing stertorously. Recording differential pressures between pulmonary artery and vein, as well as between pulmonary artery and thorax, they noticed the gradient of pressure to fall almost to zero during inspiration. During expiration the pressure gradient, before returning to normal, rises to two or three times its normal value.

In addition, Huggett[43] showed long ago that inspiratory resistance increases the cardiac output. Recently Shuler and his associates[44] have demonstrated an increase of the output of the right ventricle and a decrease of the output of the left ventricle during inspiration. These changes they attributed to the aspiration of blood into the right ventricle and to an increase in the pulmonary vascular capacity. These workers also showed that these circulatory conditions were reversed during expiration. In breathing against inspiratory resistance, however, and particularly during the slow, labored inspiration of vagotomized animals, the circulatory changes during inspiration must far outweigh those occurring during the unhampered expiration. It is clear that the abnormal circulatory dynamics accompanying labored inspiration will pro-

duce stagnation of abnormally large amounts of blood in the pulmonary vascular bed. This in turn will favor the transudation of fluid into the alveoli if a great negative intra-alveolar pressure is present at the same time.

Our further experiments showed that pulmonary edema can be produced with regularity, and in a short time, in rats breathing against inspiratory resistance while receiving normal saline intravenously at a rapid rate. The degree of pulmonary edema and the rapidity with which it occurred in these animals and in vagotomized and tracheotomized animals receiving intravenous fluids was quite comparable. Thus Farber's contention[20] that inspiratory obstruction could not have been a factor causing pulmonary edema in the short-term experiment of vagotomy plus the infusion of intravenous saline, was not sustained.

There was, however, a striking difference in the degree of pulmonary edema between the two groups of rats mentioned previously and the group of vagotomized but not tracheotomized rats. Inspiration was more labored in the animals with, than in those without, tracheotomy, which we attribute to the fact that the tracheal cannula and the system of Marriotte tubes in itself presented some resistance to inspiration, as we have pointed out previously. The degree of pulmonary edema in the nontracheotomized rats receiving intravenous fluids was small indeed. This again emphasizes the importance of inspiratory obstruction or resistance in the genesis of this type of pulmonary edema. It also stresses the role played by the tracheal cannula in producing pulmonary edema, as pointed out recently by Short,[22] and long ago by Traube, who devised a special cannula to prevent a harmful effect on the respiratory tract.

It appears that the occurrence of pulmonary edema in vagotomized animals can be best accounted for by the marked disturbances of respiration, particularly by inspiratory obstruction, which follow bilateral vagotomy. We believe, therefore, that the conclusions that have been drawn from this experimental procedure regarding the pathogenesis of pulmonary edema in patients with lesions of the central nervous system are not justified. From our studies we cannot, of course, deny that a true "neuropathic" pulmonary edema, that is, pulmonary edema due to pulmonary vasodilatation and increased capillary permeability, may exist in man. But we believe that the procedure of bilateral vagotomy furnishes no experimental proof for the existence of pulmonary edema of such pathogenesis. We, furthermore, doubt that a procedure like bilateral vagotomy, which causes such complex and hardly controllable physiologic disturbances, can be a suitable one to either definitely prove or disprove the existence of a truly neuropathic pulmonary edema.

It would seem that pulmonary edema as seen in patients may at times be due to inspiratory obstruction. Pulmonary edema of moderate degree and without demonstrable cause is often found at autopsy. This induced Cohnheim to say that many people do not die because they have pulmonary edema, but they have pulmonary edema because they die. He thought that the edema in these cases might be caused by the right ventricle continuing to work after the left has stopped. The question arises whether inspiratory obstruction caused by the accumulation of mucus, and possibly by the relaxed tongue, may be responsible

for pulmonary edema in such instances. The author has not observed clinically patients with cerebral lesions who develop pulmonary edema, and is therefore unable to say whether inspiratory obstruction occurs late during their course. The importance of preventing inspiratory obstruction in patients under general anesthesia is obvious.

SUMMARY

The pathogenesis of pulmonary edema observed in patients with lesions of the central nervous system in the absence of heart disease has never been satisfactorily explained. Some investigators believe that similar conditions exist in experimental pulmonary edema following bilateral vagotomy. They attribute this type of pulmonary edema to disturbances in the vasomotor control of the lung vessels and believe that the same factor is operating in the "neurogenic" pulmonary edema in man. Our studies on bilateral vagotomy in the rat do not support these conclusions. The evidence obtained by our work suggests that the important factor in pulmonary edema following bilateral vagotomy is inspiratory obstruction. We do not deny the possibility that "neuropathic" pulmonary edema may occur in man. However, bilateral vagotomy does not appear to furnish proof for the existence of pulmonary edema of such pathogenesis.

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THE PERIPHERAL BLOOD FLOW AND RECTAL AND SKIN TEMPERATURES IN HYPERTENSION

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THE subject of hypertension has engaged the attention of many investigators in recent years. Stimulus was given to these investigations by the experiments of Goldblatt and his associates relating to the rise in blood pressure which follows the preparation of an ischemic kidney[1, 2] and by the studies of Page[3, 4] relating to the chemical background of hypertension. The surgical treatment of hypertension, which has also increased the interest in and study of this subject, will be discussed in a succeeding paper.[5]

From an anatomic study of renal biopsies from one hundred hypertensive patients, Castleman and Smithwick[6] concluded that "the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing the hypertension. Furthermore these observations are not in keeping with the concept that renal ischemia due to pre-existing renal vascular disease is the cause of essential hypertension in man." Talbott, Castleman, Smithwick, Melville, and Pecora,[7] from a correlation of renal biopsies with renal clearance, concluded that constriction of efferent glomerular arterioles was not present in the early stage of renal vascular disease.

Pickering[8] found the rate of blood flow through the forearm in hypertensive subjects the same as that in subjects with normal blood pressure and concluded that, owing to vasoconstriction, the resistance offered by the vessels of the forearm is increased in hypertension. Prinzmetal and Wilson[9] also found that the resting blood flow in the arm was within normal limits and concluded that increased vascular resistance is not confined to the splanchnic area but is generalized throughout the systemic circulation. Abramson and Fierst,[10] using the venous occlusion plethysmographic method, found that the resting blood flow through the arm and leg was significantly greater, but that through the hand was less in hypertensive subjects than in normal subjects. They concluded that their observations directly contradicted the prevailing theory that there is generalized and uniformly increased peripheral resistance in hypertension.

One of the results of these studies has been the accumulation of a vast amount of literature which has contributed much to the understanding of hypertension. However, the mechanism of hypertension, whether it is of nervous or humoral origin, still remains unexplained. It appeared to us that a study of the total peripheral blood flow in essential hypertension might be of interest in

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the whole general problem as there are conflicting views about the blood flow in local areas. We have accordingly measured the amount of blood allotted to the peripheral circulation in patients suffering from essential hypertension. These observations form the basis of this report. In another paper the effects on the peripheral blood flow of splanchnic resection for the lowering of blood pressure will be appraised.[5]

Sixty-nine observations were made on 56 patients who had arterial hypertension; 25 were men, and 31 were women. The ages ranged from 19 to 66 years.

METHODS

The peripheral blood flow was measured by our modification[11, 12] of the method of Hardy and Soderstrom.[13] Hardy and Soderstrom have shown that, at a temperature below 28° C., the skin functions like a dead insulator when the subject is lying nude in the basal state, and that blood flow to the skin, thermal conductivity of the peripheral tissues, and vaporization are constant and minimum. With an increase in blood flow to the periphery, more heat is brought from the deeper tissue to the surface. This increases the thermal conductance of the superficial tissues; therefore, changes in thermal conductance become an index of peripheral blood flow. With this method, blood flow is expressed as a function of heat loss, surface area, *average weighted skin temperature,* and rectal temperature. The method requires the recording of skin and rectal temperature[13] at known intervals, oxygen consumption,[14] height, and body weight.[15, 16] The skin temperatures were recorded with a Hardy-Soderstrom radiometer[13] from eleven points on the anterior surface of the body as shown in Fig. 1. With this method the amount of blood allocated to the whole periphery of the body is measured, rather than the flow in local areas, and may be expressed in cubic centimeters per square meter of body surface per minute.

Plan of Procedure.—The plan of procedure was that described in recent publications.[12, 17] All measurements were carried out in the morning before breakfast with the patients in a basal metabolic state. They were brought to the constant temperature room and allowed to lie in bed nude, covered only with a sheet. One hour was allowed for adjustment to the room temperature of 27° C. and 50 per cent humidity. Measurements of skin and rectal temperatures were made at twenty-minute intervals. Each set of observations covered a period of sixty to one hundred minutes. Blood pressure and pulse rate were recorded between temperature readings. The basal metabolic rate was measured at the beginning and again at the end of the morning's observations.

Four to six sets of skin and rectal temperatures were recorded from which three to five estimations of peripheral blood flow could be made for the morning. The data recorded in Table I for each date show the averages of the peripheral blood flows, temperatures, blood pressures, and heart rates for the morning.

OBSERVATIONS

The results of the observations are shown in Table I and Fig. 1.

Peripheral Blood Flow.—The average peripheral blood flow of the whole group was 57 c.c. per square meter of body surface per minute, as compared

with 73 c.c. per square meter per minute for a group of normal young male subjects[18] at the same room temperature (Table I, Fig. 1). While the peripheral blood flow is statistically significant in the group of normal young adults, the fluctuations in the hypertensive groups are such that the difference from the young normal male group is not significant. There was no significant difference in the peripheral blood flow in the men of the hypertensive group as compared

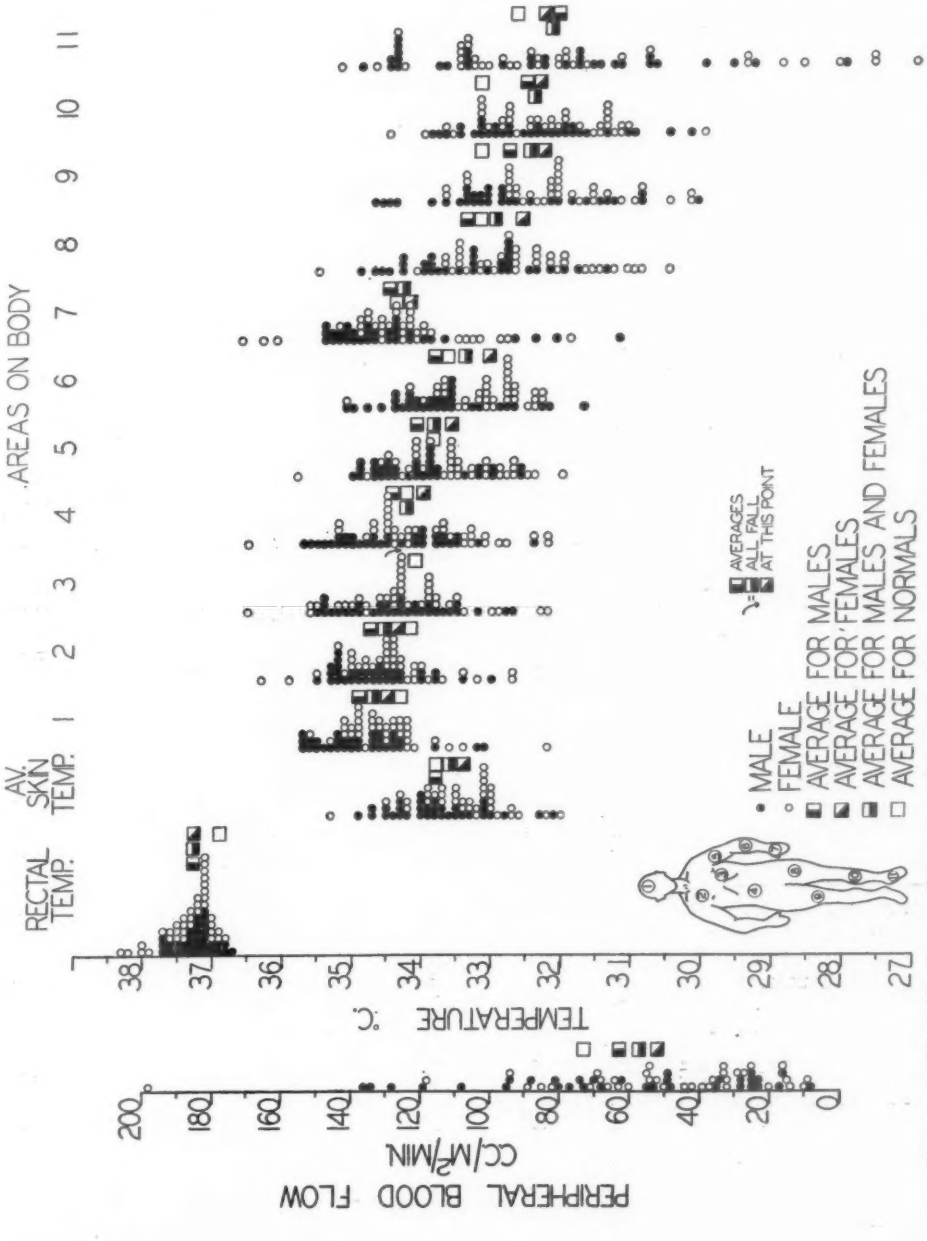

Fig. 1.—In this figure are shown the peripheral blood flows and rectal and skin temperatures of patients suffering from hypertension. Each open (female) and closed (male) circle represents the average of the morning's observations on one patient (Table I). The averages for all the men, all the women, and of both are shown by appropriate symbols. The average for normal men[18] is shown for comparison. The figure also serves as a series of frequency diagrams.

TABLE I. OBSERVATIONS RELATING TO THE PERIPHERAL BLOOD FLOW IN PATIENTS SUFFERING FROM HYPERTENSION

CASE, HISTORY NO., SEX, AGE (YR.)	DATE	PERIPHERAL BLOOD FLOW (C.C./M.²/MIN.)	AVERAGE RECTAL TEMPERATURE ° C.	AVERAGE WEIGHTED SKIN TEMPERATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
					1 ° C.	2 ° C.	3 ° C.	4 ° C.	5 ° C.	6 ° C.	7 ° C.	8 ° C.	9 ° C.	10 ° C.	11 ° C.				
Data Relating to Twenty-Five Male Subjects																			
C. W. 385437 M. 42	6/17/44	55	37.33	33.77	35.7	35.2	34.1	33.8	34.9	33.7	35.4	32.8	33.3	31.7	32.3	205/122	80	+12	Hypertension. Slightly enlarged heart
G. W. 386933 M. 48	6/19/44	28	37.67	33.06	34.7	34.4	34.0	33.8	33.8	33.6	33.9	32.4	30.9	31.1	31.6	251/162	98	+34	Hypertension. Enlarged heart. Aortic insufficiency. Myocardial infarct. Arteriolar nephrosclerosis
C. C. 386438 M. 40	6/3 /44	48	37.06	33.90	35.2	34.9	34.2	33.7	34.2	34.4	35.0	32.8	32.9	32.6	34.4	218/139	89	+ 5	Essential hypertension. Enlarged heart
R. R. 388459 M. 47	6/23/44	35	37.73	33.94	35.7	35.5	34.9	34.5	34.6	34.1	35.3	32.8	32.7	32.2	31.3	217/131	80	+13	Hypertension
R. B. 301492 M. 25	7/18/41	95	37.51	34.03	34.4	34.6	34.5	34.7	33.9	33.8	34.9	33.9	33.2	33.0	33.4	170/106	72	+11	Hypertension
B. O'B. 292901 M. 22	4/ 5/41	23	37.21	33.26	35.2	34.0	34.6	34.5	34.1	33.8	34.7	32.9	31.3	31.9	28.0	128/98	69	- 4	Hypertensive cardiovascular disease
D. S. 339187 M. 47	10/ 9/42	68	37.62	33.09	34.4	33.8	33.9	34.1	33.2	32.9	32.4	33.3	32.1	32.3	30.7	211/128	73	± 0	Hypertension
E. S. 268711 M. 41	6/22/40 6/24/40	17 28	37.51 37.15	32.83 32.98	33.8 33.2	34.4 33.8	33.9 33.8	34.0 33.7	33.2 33.0	33.3 32.3	34.5 34.4	32.2 31.8	30.9 31.7	30.5 31.4	31.8 34.5	190/139 164/119	94 84	+20 +13	Hypertension. Probable coronary occlusion

H. S. 372225 M. 32	12/17/43	8	37.02	33.70	35.0	34.5	33.2	33.6	34.0	33.3	34.9	32.8	32.9	33.5	33.8	158/108	66	- 8	Hypertension. Hydronephrosis. Enlarged heart
J. O'K. 231295 M. 40	3/10/43 3/20/43	77 23	37.68 37.44	34.28 34.36	35.5 35.5	35.2 35.2	35.4 35.5	35.3 35.4	34.7 34.7	34.4 34.6	35.1 35.4	34.3 34.3	33.1 33.1	32.4 32.0	32.0 32.3	181/126 181/117	88 75	+19 -12	Hypertension
C. W. 331023 M. 48	7/ 2/42	80	37.24	33.55	34.3	34.8	34.1	34.8	34.6	34.0	31.2	33.3	32.5	31.8	30.0	186/116	85	+ 5	Hypertension
H. V. 281681 M. 40	10/20/42	49	37.59	33.96	34.9	34.6	35.1	34.9	34.4	33.9	34.2	34.7	32.8	32.8	30.8	173/136	82	+22	Hypertension. Enlarged heart
H. O. 381111 M. 44	4/11/44	25	37.34	32.06	33.1	33.0	32.7	32.4	32.6	31.7	32.1	31.4	31.5	31.0	31.2	186/126	63	+ 5	Hypertension. Slightly Enlarged heart. Hypertensive encephalopathy
N. C. M. 36	5/ 6/44	34	36.68	33.65	34.3	34.5	33.5	34.2	33.0	32.8	34.4	33.5	33.4	33.1	32.9	132/86	66	-11	Hypertension
A. R. 249201 M. 40	4/23/40 5/ 1/40	73 74	37.11 36.92	33.49 33.77	35.1 34.7	34.6 34.3	34.6 33.6	34.5 34.0	34.5 33.9	34.1 33.7	34.4 34.5	33.3 33.3	33.4 33.9	31.9 33.1	29.6 33.4	187/124 127/96	69 68	-11 -11	Hypertension. Enlarged heart
W. M. 224740 M. 26	2/ 6/39 2/ 8/39	94 134	37.28 37.25	34.68 34.66	35.7 35.6	35.3 35.2	35.4 35.3	35.7 35.5	34.9 35.0	35.1 35.0	35.1 35.3	34.3 34.5	34.6 34.5	33.5 33.3	31.8 32.5	201/139 196/135		+22 +10	Malignant hypertension
A. B. 256256 M. 19, 21, 23 resp't.	2/14/40 3/25/42 6/16/44	128 49 88	37.24 37.12 36.99	34.25 33.81 34.24	35.1 34.5 34.6	35.3 35.0 35.2	35.4 35.2 34.3	35.6 35.1 35.2	34.7 34.1 33.9	34.2 33.6 33.6	34.0 33.7 34.8	34.9 33.9 34.0	33.4 33.1 32.9	33.8 32.8 33.2	30.8 29.3 34.9	173/124 196/127 205/141	68 59 73	- 4 - 6 +11	Hypertensive cardiovascular disease. Malignant hypertension. Encephalopathy
F. B. 316266 M. 37	1/ 8/42	53	37.23	33.44	34.6	34.7	34.3	34.1	34.5	33.9	34.4	32.8	31.4	32.0	31.8	181/130	86	+ 5	Hypertension. Arteriolar nephrosclerosis. Cardiac insufficiency. Chronic passive congestion of liver, spleen, and lungs
P. L. 319076 M. 24	3/ 1/42	16	37.20	33.07	34.6	34.0	33.5	34.0	32.6	34.7	34.8	32.5	31.9	32.4	30.8	168/121	67	-22	Hypertensive cardiovascular disease
T. G. 311596 M. 13	1/ 5/42	119	37.07	34.47	35.2	34.9	34.9	35.0	34.1	34.3	35.2	33.8	33.7	33.9	34.4	146/116	92	- 9	Hypertension

TABLE I—CONT'D

CASE, HISTORY NO., SEX, AGE (YR.)	DATE	PERIPHERAL BLOOD FLOW (C.C./M.²/MIN.)	AVERAGE RECTAL TEMPERATURE °C.	AVERAGE WEIGHTED SKIN TEMPERATURE °C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
					1 °C.	2 °C.	3 °C.	4 °C.	5 °C.	6 °C.	7 °C.	8 °C.	9 °C.	10 °C.	11 °C.				
Data Relating to Twenty-Five Male Subjects—Cont'd																			
W. C. 375325 M. 48	1/ 5/44 1/ 7/44	62 70	37.27 37.10	34.30 33.97	35.3 35.0	35.1 34.8	34.5 34.3	34.7 34.3	34.4 33.4	34.2 34.2	35.0 34.8	33.7 32.9	33.5 33.2	33.2 33.9	34.4 34.5	198/113 193/112	66 66	- 1 - 2	Hypertension. Slightly enlarged heart
R. L. 376206 M. 19	2/10/44	81	36.81	33.97	34.7	34.7	34.4	34.6	33.9	33.6	35.1	33.9	33.3	32.5	33.4	212/136	82	- 5	Hypertension. Chronic glomerulonephritis. Enlarged heart
S. McD. 95209 M. 48	12/ 3/43	25	37.11	33.52	34.9	33.5	33.7	33.5	33.9	33.6	34.2	33.1	32.2	33.0	32.5	177/113	68	-11	Hypertension. Enlarged heart
V. K. 308001 M. 51	4/ 5/44	25	36.94	32.25	34.4	34.3	32.8	32.2	33.4	32.3	32.7	32.0	30.1	30.2	31.5	243/121	91	+33	Hypertension. Enlarged heart. Arteriosclerotic heart disease. Hyperthyroidism
G. L. 351331 M. 31	3/16/43 3/22/43	136 108	37.36 37.11	34.89 34.51	35.6 35.4	35.3 35.0	35.0 34.7	35.1 35.0	34.9 34.5	34.8 34.4	35.3 35.1	34.6 34.0	34.7 34.4	33.7 33.2	34.4 34.4	156/108 163/113	68 67	+ 6 + 3	Essential hypertension
Average—men Average age = 36 yr.		61	37.27	33.74	34.8	34.7	34.3	34.4	34.1	33.8	34.5	33.4	32.8	32.5	32.1	184/122	76	+ 4	
Standard deviations about the means		54	0.24	0.60	0.7	0.6	0.8	0.8	0.7	0.8	1.0	0.9	1.1	1.0	1.7	28/15	11		
Data Relating to Thirty-One Female Subjects																			
E. E. 375575 F. 56	2/10/44	69	37.16	33.66	34.2	34.1	34.3	33.7	34.3	33.2	34.0	32.9	33.2	33.2	33.3	193/124	82	- 2	Hypertension. Enlarged heart. Cerebral hemorrhage
R. S. 381016 F. 50	4/ 4/44	16	37.23	33.17	34.7	34.1	32.9	32.8	32.9	33.0	34.6	32.0	32.8	32.8	33.5	182/118	71	- 4	Essential hypertension

M. D. 384959 F. 46	5/29/44	63	37.06	33.49	34.5	34.4	34.3	34.5	33.6	33.1	34.7	32.2	32.1	32.2	33.4	172/110	69	± 0	Hypertension. Arteriolar nephrosclerosis
S. C. 384676 F. 33	5/27/44	32	37.22	33.11	34.3	33.7	33.6	33.1	33.5	32.7	34.4	32.4	32.2	32.1	33.2	150/107	73	- 4	Essential hypertension. Enlarged heart
C. N. 386907 F. 42	5/31/44	71	37.38	33.92	35.1	35.0	34.9	33.4	34.1	33.7	35.4	33.1	33.4	31.9	32.9	140/85	66	+ 1	Essential hypertension. Enlarged heart
A. A. 318945 F. 41	2/27/42	39	37.35	33.54	34.4	34.8	34.5	34.7	32.9	33.7	34.8	33.5	32.1	31.6	32.0	208/116	73	-10	Hypertension. Bronchial asthma. Enlarged heart
M. J. 315435 F. 43	1/ 3/44	82	37.53	34.51	35.1	35.1	35.1	35.2	34.6	34.2	35.2	34.1	33.7	33.6	33.7	241/126	65	- 2	Hypertension. Hypertensive encephalopathy. Enlarged heart
I. H. 287756 F. 26	4/11/44	33	37.47	32.01	32.2	32.7	32.3	32.4	32.4	32.4	32.9	31.6	31.2	31.2	31.2	221/148	85	+30	Hypertension
B. G. 311888 F. 25	11/10/41	33	37.64	32.71	35.0	34.9	34.8	34.2	33.6	32.8	33.3	31.3	30.5	30.0	29.4	177/116	92	+14	Essential hypertension. Enlarged heart
C. C. 311597 F. 44	1/ 5/42	32	37.08	33.26	34.5	34.5	35.6	34.1	33.1	33.4	34.4	32.7	32.4	32.0	27.6	169/117	79	- 4	Essential hypertension
O. K. 368408 F. 38	1/12/44	60	37.92	33.85	35.0	34.6	35.0	34.4	34.1	33.2	34.1	33.2	32.8	33.2	31.7	209/132	78	- 5	Essential hypertension
C. D. 372511 F. 25	12/ 7/43	42	38.20	34.25	35.1	35.9	35.5	35.2	34.5	33.2	34.9	33.6	32.8	33.2	32.1	184/137	70	- 6	Hypertension. Enlarged heart. Rheumatic heart disease. Mitral stenosis and insufficiency
L. H. 351566 F. 44	2/ 1/44	64	37.25	33.87	35.3	34.5	34.4	34.4	34.8	33.8	35.2	32.2	32.8	32.3	34.3	166/111	74	+ 2	Hypertension. Enlarged heart
E. C. 380212 F. 46	3/24/44	118	37.34	34.17	34.6	35.5	34.4	34.8	34.2	33.7	34.9	33.7	33.2	32.8	34.4	182/116	72	+12	Essential hypertension. Enlarged heart

TABLE I—CONT'D

CASE, HISTORY NO., SEX, AGE (YR.)	DATE	PERIPHERAL BLOOD FLOW (C.C./M.²/MIN.)	AVERAGE RECTAL TEMPERATURE ° C.	AVERAGE WEIGHTED SKIN TEMPERATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
					1 ° C.	2 ° C.	3 ° C.	4 ° C.	5 ° C.	6 ° C.	7 ° C.	8 ° C.	9 ° C.	10 ° C.	11 ° C.				
Data Relating to Thirty-One Female Subjects—Cont'd																			
E. L. 233250 F. 43	4/27/39	50	37.24	32.70	33.8	34.0	33.5	33.3	32.0	32.7	33.4	32.0	31.4	31.3	32.4	220/130		-27	Essential hypertension. Slight cardiac enlargement
	5/ 6/39	37	37.12	32.61	33.4	34.2	33.8	33.3	32.5	32.8	33.2	31.0	30.9	31.4	32.4	214/112		+ 5	
M. N. 231336 F. 33	4/28/39	52	37.39	33.53	34.3	34.4	34.4	34.5	33.7	33.8	34.2	33.5	32.7	31.2	32.5	230/130		+16	Hypertension. Enlarged heart
T. W. 243332 F. 39	2/29/40	198	37.64	35.34	35.6	36.3	36.5	36.5	35.8	35.1	35.6	35.5	33.7	34.0	33.5	227/129	71	+22	Hypertension. Enlarged heart
M. H. 250110 F. 33	11/10/39	66	37.08	33.73	34.8	34.5	35.2	35.2	33.6	33.4	33.5	33.4	31.6	31.4	27.6	219/129	96	+ 8	Hypertension. Slight cardiac enlargement
A. P. 385261 F. 23	6/15/44	85	36.83	33.67	34.9	35.2	34.2	33.8	33.9	33.1	34.3	32.8	31.9	33.2	33.1	171/115	71	+ 7	Hypertension
C. F. 256800 F. 33	6/12/44	14	36.88	33.02	34.1	33.8	34.0	32.9	33.3	32.8	34.6	31.7	32.3	32.4	31.9	131/96	74	-10	Hypertension
D. B. 304744 F. 30	9/13/41	20	37.16	33.05	34.2	34.7	35.6	34.5	32.7	32.2	31.9	33.7	32.1	31.8	27.0	146/120	76	- 9	Essential hypertension
R. M. 382365 F. 52	3/31/44	54	36.73	33.43	34.4	34.3	34.3	33.1	33.5	33.1	34.3	32.7	32.1	32.8	33.5	208/125	67	+ 7	Hypertension. Enlarged heart
R. McK. 376846 F. 46	2/17/44	29	37.01	33.43	34.9	34.1	33.9	33.4	33.3	33.1	34.6	32.4	32.7	32.5	33.5	170/108	76	-13	Essential hypertension. Enlarged heart. Encephalopathy
	2/18/44	44	36.92	32.98	34.9	33.4	33.4	33.4	32.7	32.5	34.3	30.9	31.0	32.2	32.8	155/106	72	-18	

F. 46	2/18/44	44	36.92	32.98	34.9	33.4	33.4	33.4	32.7	32.5	34.3	30.9	31.0	32.2	32.8	155/106	72	-18	heart. Encephalopathy

M. I.																			
369586	1/19/44	15	37.10	32.24	34.2	32.7	32.2	32.2	33.1	32.8	34.6	30.5	30.2	34.5	33.3	159/124	84	+ 6	Cushing's syndrome. Hypertensive cardiovascular disease. Generalized arteriosclerosis. Arteriosclerotic heart disease. Myocardial infarct. Enlarged heart. Aortic insufficiency. Fibrosis of lungs
F. 26	2/ 7/44	25	37.08	33.11	34.2	33.2	33.0	33.2	33.6	33.0	34.9	31.1	31.8	32.7	34.7	168/108	64	- 8	
A. B.																			
373431	12/14/43	94	37.72	34.19	33.6	35.0	34.3	34.7	34.4	33.5	34.8	33.5	33.4	33.7	35.2	232/187	82	+28	Hypertension. Enlarged heart. Chronic glomerulonephritis
F. 43																			
M. K.																			
373552	12/ 8/43	36	37.99	33.14	34.9	34.5	34.3	33.6	33.6	32.8	34.5	32.1	31.6	31.4	32.1	186/129	98	+13	Hypertension. Enlarged heart
F. 39																			
S. S.																			
373586	12/10/43	10	37.98	32.90	34.7	34.3	33.9	33.3	33.5	32.3	33.9	33.2	32.1	31.5	28.9	180/114	72	+ 9	Hypertension. Enlarged heart
F. 47	12/15/43	9	38.29	33.00	34.9	34.4	33.9	33.5	34.0	33.3	34.2	32.4	32.2	31.4	29.4	174/111	68	+ 5	
J. M.																			
237987	11/11/42	89	37.31	32.98	34.2	33.4	33.8	33.7	32.8	32.6	34.0	31.5	32.2	32.1	32.7	154/85	72	+ 6	Arteriosclerotic heart disease. Hypertension. Enlarged heart
F. 66																			
L. M.																			
342091	11/19/42	68	37.54	33.78	34.5	34.4	34.6	34.3	34.1	34.0	34.2	33.5	32.1	32.9	33.4	172/109	66	- 4	Hypertension
F. 37																			
N. L.																			
340799	10/22/42	55	37.42	33.24	34.3	33.9	34.8	34.2	32.7	32.7	32.8	33.0	31.6	32.5	32.0	164/111	72	+ 1	Chronic glomerulonephritis. Hypertension
F. 25																			
M. T.																			
229483	3/ 8/44	27	37.02	33.12	34.6	34.4	34.3	34.5	33.6	33.1	34.2	32.7	32.6	31.5	28.1	133/84	76	+ 4	Essential hypertension
F. 49	3/ 9/44	54	36.96	33.25	34.7	34.8	33.9	34.5	34.1	32.8	34.1	32.7	32.8	32.0	28.6	132/84	75	+ 4	
Average—women		52	37.27	33.46	34.5	34.3	34.3	34.0	33.6	33.1	34.2	32.6	32.3	32.4	32.2	182/120	75	+ 2	
Average age = 39 yr.																			
Standard deviations about the means		43	0.38	0.68	0.6	0.7	0.9	0.9	0.7	0.6	0.7	1.0	0.9	0.9	2.2	30/19	8		
Average—men and women																			
Age = 38 yr.		57	37.27	33.59	34.7	34.5	34.3	34.2	33.8	33.4	34.3	33.0	32.5	32.4	32.1	183/121	76	+ 3	
Standard deviations about the means		43	0.33	0.63	0.6	0.7	0.8	0.9	0.8	0.8	1.6	1.0	1.0	0.9	1.9	32/16	9		
Average—normal men		73	36.79	33.74	34.4	34.2	34.1	34.2	33.8	33.7	34.4	33.2	33.2	33.2	32.7	105/71	61	- 5	
Standard deviations about the means		30	0.16	0.33	0.3	0.4	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.5	1.9	5/5	7	10	

with the group of normal young adults, or in the peripheral blood flow of the men of the hypertensive group as compared with the women with hypertension.

Average Rectal Temperature.—The average rectal temperature for the hypertensive patients was 37.27° C., with a range of 36.68° C. to 38.29° C., while the average rectal temperature of normal young subjects was 36.79° C., with a range of 36.32° C. to 37.24° C. Although on statistical analysis the difference is not significant, the rectal temperature of hypertensive patients was higher than that of normal persons (Table I, Fig. 1); most of the hypertensive patients have rectal temperatures above 37°, while most of the normal persons have rectal temperatures below 37°.

Average Weighted Skin Temperature.—The average weighted skin temperature of the whole body of the hypertensive patients was 33.59° C., with a range of 32.01° C. to 35.34° C., while the average for the normal young subjects was 33.74° C., with a range of 32.65° C. to 34.36° C.[18] (Table I, Fig. 1.) In short the mean of the average weighted skin temperature of the hypertensive patients was cooler than that of normal young subjects, but the difference is not statistically significant.

Temperature of Hands.—The average of the temperatures of the hands in hypertensive patients was 34.3° C., with a range of 31.2° C. to 35.4° C., while the average temperature for the normal young subjects was 34.4° C., with a range of 32.8° C. to 35.5° C.[18] (Table I, Fig. 1). That is to say the hand temperatures in the group with hypertension were essentially the same as those of the normal subjects, but the fluctuations were greater.

Temperature of the Feet.—The average of the temperatures of the feet in hypertensive patients was 32.1° C., with a range of 27.0° C. to 35.2° C., as compared with an average temperature of 32.7° C., with a range of 26.0° C. to 34.3° C., in normal subjects[18] (Table I, Fig. 1). In short, the foot temperature of hypertensive patients was slightly colder, but because of the wide fluctuations of the foot temperature in individuals (emotional effects, etc.) the difference is not statistically significant.

Temperature of Forehead.—The temperature of the forehead in hypertensive patients averaged 34.7° C., with a range of 32.2° C. to 35.7° C., as compared with an average of 34.4° C., with a range of 33.8° C. to 34.9° C, for the normal group[18] (Table I, Fig. 1). In short, the forehead was slightly warmer in hypertensive patients than in normal young subjects, but the difference is not statistically significant.

Temperatures of Areas of the Body Considered as Regions.—When the temperature of the individual areas of the body are considered in relation to each other, it is seen that the temperature of the upper part of the body, including the forehead (Area 1), upper chest (Area 2), and lower chest (Area 3), is warmer in hypertensive than in normal subjects.[18] The temperature of the abdomen (Area 4), arm (Area 5), and hand (Area 7) is essentially the same in those with hypertension as in normal subjects. The temperature of the lower part of the body, including the forearm (Area 6), upper thigh (Area 8), lower thigh (Area 9), leg (Area 10), and foot (Area 11), however, are colder in the

hypertensive subjects than in the normal subjects (Table I, Fig. 1). Although these differences are not significant statistically, it appears more than chance that in both men and in women with hypertension the upper part of the body is warmer and the lower part is cooler. It would not be expected that the means should take such a precise arrangement if it were the result of chance. The reduction in temperature of the lower part of the body is greater than the elevation of temperature of the upper part of the body, so that the average of the weighted skin temperature is, on the whole, less in the hypertensive patients.

Blood Pressure.—The average of the blood pressures for this hypertensive group was 183/121 (Table I).

Pulse Rate.—The average of the pulse rates of this hypertensive group was 76 per minute (Table I).

Basal Metabolic Rate.—The average of the basal metabolic rates of the group with hypertension was +3 per cent, while that of the normal subjects was –5 per cent [18] (Table I, Fig. 2).

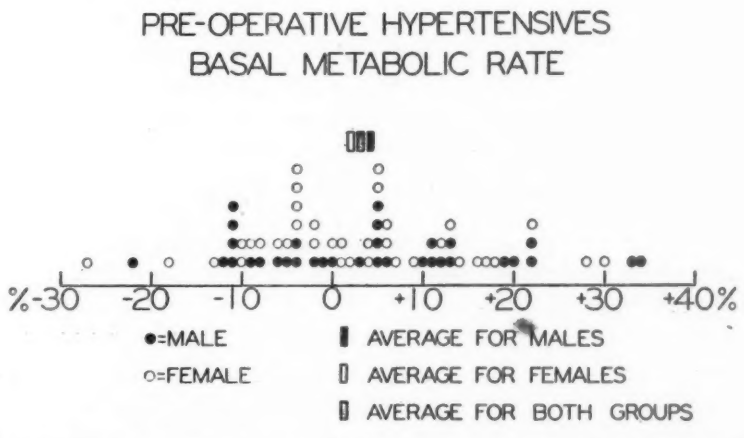

Fig. 2.—In this figure is shown the scatter of the basal metabolic rates of the patients whose data are shown in Fig. 1.

DISCUSSION

These observations show certain differences in the peripheral blood flow and rectal and skin temperatures of hypertensive subjects as compared with those of young normal subjects. We did not have a comparable mixed group of normal young men and women for comparison but have used the young male group on which observations have already been reported. On comparison of the male component of this group of hypertensives with the group of normal men, it was found that these show the same trends as in the average of the male and female hypertensive groups, but the differences were slightly less marked. The trend is for a lower peripheral blood flow in the hypertensive group than in normal subjects, that the hand (Area 7), abdomen (Area 4), and arm so. The room temperature of 27° C. was chosen in order to have vasodilatation present in each series. The rectal temperature was higher in the hypertensives

than in normal subjects, but the average weighted skin temperature was less. The hands were of the same temperature in the hypertensive patients as in the normal persons, but the feet were colder. The foreheads of the hypertensive patients were slightly warmer than normal, but the difference was not sufficient to explain the flush which hypertensive patients exhibit clinically.

It is seen that the upper part of the body is warmer in hypertensive than in normal subjects, that the hand (Area 7), abdomen (Area 4), and arm (Area 5), have the same temperature in hypertensive and normal individuals; and that the lower part of the body, including the forearm (Area 6), upper thigh (Area 8), lower thigh (Area 9), leg (Area 10), and foot (Area 11), is colder than normal. The reduction in temperature in the lower part of the body is greater than the elevation of temperature in the upper part. As a consequence, the average weighted skin temperature is colder in hypertensive patients than in normal subjects when the whole group is considered; for the male group alone, however, the average skin temperature was the same as in the normal group. The warmer upper part indicates increased peripheral blood flow to this part, the normal temperature of the middle part of the body indicates an essentially normal amount of blood flow in this area, and the cold lower part of the body indicates a decreased amount of blood allotted to the peripheral circulation in this part. Reduction in temperature of the colder part is so much more marked than the rise in temperature of the warmer part, taking into consideration weighting of different parts of the body, that the total amount of blood allotted to the whole periphery of the body is decreased as compared with a normal subject. There appears then to be vasodilatation in the upper part of the body and vasoconstriction in the lower part. As a consequence, the skin cannot dissipate efficiently the increased amount of heat produced, and increased heat storage and rise in rectal temperature result.

Abramson and Fierst[10] found the resting blood flow to the forearm and leg of hypertensive patients by the venous occlusion method was greater while that in the hand was less than in a normal group they observed. This method measures the total amount of blood going to that part in cubic centimeters per minute per 100 c.c. of limb volume. On the other hand, the method we have used measures the average amount of blood allotted to the periphery of the whole body in cubic centimeters per square meter of body surface per minute, for a depth of about 1 cm. below the skin surface. Steele and Kirk[19] in a study of nine hypertensive patients did not find any difference from normal in the skin temperature in the areas from which they recorded the temperature. Differences in the general plan and technique of the two sets of experiments may account for these differences: our patients were nude and remained basal throughout the morning the observations were made; moreover the larger number of patients in our series may give a wider spread of variations.

In these patients with hypertension there is a linear correlation between peripheral blood flow and the average weighted skin temperature (Fig. 3) since the higher average skin temperatures were associated with higher values for the peripheral blood flow. There was no demonstrable correlation between periph-

eral blood flow and rectal temperature in these subjects, nor between systolic or diastolic levels of blood pressure and peripheral blood flow.

The average of the basal metabolic rates for the whole series of hypertensive patients was +3 per cent, compared with an average of –5 per cent in normal men. The range in both from minus to plus basal metabolic rates was slightly greater in the hypertensive series, but the basal rate in hypertension does not appear to be appreciably greater than in normal subjects[18] or in other patients with heart disease before the onset of failure.[20] These observations are in agreement with those of Shapiro[21] who found that the basal metabolic rate in hypertension falls within accepted normal limits.

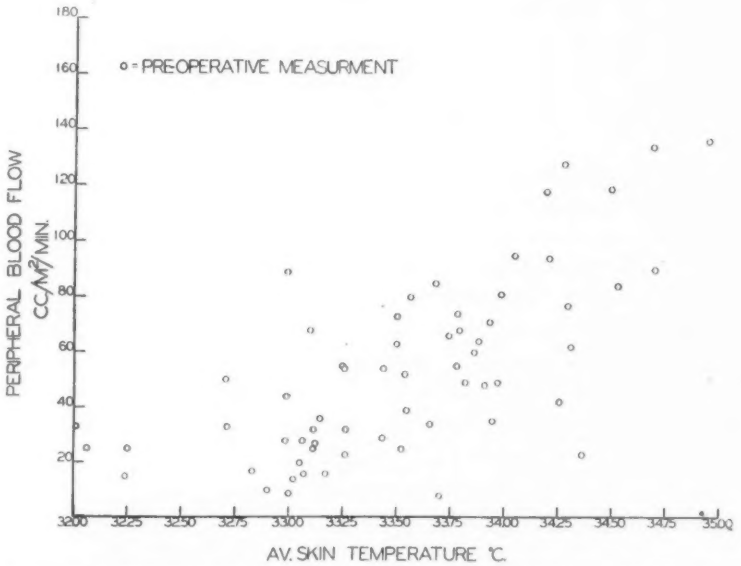

Fig. 3.—In this figure the peripheral blood flows of all patients (Table I) are plotted against the corresponding average skin temperatures. A linear correlation is demonstrated, which, however, is not as close as the correlation after operation.[5]

It is of interest to compare the data relating to the male subjects in this younger group of hypertensive patients with the hypertensive male patients in the later decades.[22] The peripheral blood flow in the younger subjects was *lower* than in the older ones but not significantly so statistically. The rectal and average weighted skin temperatures were *higher* in younger hypertensive patients, but again the difference was not great enough to be significant. With a few exceptions the temperatures for all the areas of the body were greater in the younger group of hypertensive patients. The exceptions were the temperatures of the hand (Area 7), which were decreased, and of the lower thigh (Area 9) and leg (Area 10), which were the same. The differences, however, were not significant. Although on statistical analysis the differences are not significant, there is the pattern in which there appears to be a trend toward lower peripheral blood flow and greater rectal and skin temperatures in young hypertensive patients than in those with hypertension who reach the later decades. In short,

the deviation from the normal is not as great in older individuals with hypertension as in the younger hypertensive patients.

It is of interest to compare the measurements in patients suffering from essential hypertension with those made in patients in whom hypertension was a consequence of coaretation of the aorta.[23] The data in the two sets of observations are not strictly comparable, because in the latter group observations were made at 25° C., while in the observations now being reported the room temperature was 27° C. In the patients with coaretation of the aorta the average weighted skin and rectal temperatures were higher than those in normal subjects at the same room temperature, and, moreover, the temperatures of the skin of all the eleven areas of the body which were measured were *higher* than those in normal subjects. The hypertension of coaretation of the aorta is associated with warm feet and that of essential hypertension is associated with cool feet. The cardiac output in coaretation of the aorta is increased[24] so that there is available an increased amount of blood for allotment to the periphery of the body.

Starr and his associates[25] and Stewart[26] have shown that in certain patients with hypertension without heart failure the cardiac output is within the normal range, while in others the cardiac output is decreased. Starr found that those patients with the smaller cardiac output had smaller hearts than those with large outputs. In some, the cardiac output was smaller than that in subjects with normal hearts. This reduced cardiac output achieves the maintenance of hypertension without increase in the heart's basal work. Since measurements of cardiac output were not available in the group of patients we are now reporting, correlation with the trend toward decrease in peripheral blood flow could not be made.

The manifestations of the high blood pressure of essential hypertension are also different from those in the hypertension of pheochromocytoma. In a patient suffering from such a tumor, observations[27] pointed to marked generalized peripheral vasoconstriction. The peripheral blood flow was decreased even though the basal metabolic rate was +48 per cent which would be expected to increase the peripheral blood flow (Stewart and Evans[28]). The average weighted skin temperature was decreased (32.45° C.), and the temperature of the hands and feet was very cold (31.10° C. and 26.80° C., respectively). Because the body could not dissipate the increased amount of heat produced, there was heat storage and a high rectal temperature resulted.

These observations indicate that the elevation of arterial pressure in hypertensive individuals does not depend on constriction of the arterioles of the skin, subcutaneous tissue, and muscle to the depth of 1 cm. below the surface. Steele and Kirk[19] arrived at a similar conclusion. While on the average the peripheral blood flow may be decreased in hypertension, there is no correlation between the peripheral blood flow and the level of blood pressure. Moreover, if the rise in blood pressure were dependent on such vasoconstriction, which would presumably be generalized, it would be difficult to explain the tendency to increase in warmth of the upper part of the body and decrease in temperature of the lower part in hypertensive individuals. On the other hand, in the hyper-

tension of pheochromocytoma[27] in which there is reason to believe that there is vasoconstriction due to the discharge of epinephrine into the blood stream, the effects would be expected to be generalized. In accord with this theory, we found[27] that the skin in most parts of the body was colder than normal, with a low average weighted skin temperature and very cold forehead, hands, legs, and feet.

SUMMARY

The peripheral blood flow and average skin and rectal temperatures have been measured under basal conditions in 56 patients suffering from arterial hypertension. A modification of the method of Hardy and Soderstrom was used. Observations were made at an environmental temperature of 27° C. and 50 per cent humidity.

1. The average peripheral blood flow for the group is slightly decreased as compared with normal subjects, but the difference does not appear to be statistically significant; the range is essentially the same as in normal subjects.

2. The rectal temperature is higher than in normal subjects, the temperature being over 37° C. in most hypertensive subjects and under 37° C. in the normal control group.

3. The average weighted skin temperature is lower than that in normal subjects, but the difference is not significant statistically.

4. In hypertensive patients the temperature is higher than normal in the upper part of the body, is near the normal level in the middle part of the body, and is cooler than normal in the lower part, especially in the feet.

5. There were no significant differences between the peripheral blood flow or rectal or skin temperatures of the men and those of the women with hypertension.

6. The level of the peripheral blood flow is unrelated to the level of the systolic or diastolic blood pressure in individual patients, and a linear correlation between peripheral blood flow and blood pressure level was not apparent.

7. In these patients with hypertension there was a linear correlation between the level of peripheral blood flow and the average weighted skin temperature, in that the higher the skin temperature the higher the peripheral blood flow.

8. The basal metabolic rate in hypertensive patients is within the normal range.

9. The hypertension of patients observed in this study exhibits different characteristics from those prevailing in coarctation of the aorta and in pheochromocytoma, in which the local skin temperatures are, respectively, warmer and cooler than normal.

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AN EVALUATION OF THE USE OF MULTIPLE VERSUS SINGLE PRECORDIAL LEADS, IN CONJUNCTION WITH THE THREE LIMB LEADS, FOR PRACTICAL CLINICAL ELECTROCARDIOGRAPHY

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THE value of precordial leads in clinical electrocardiography has been clearly established through numerous studies and extensive practical experience since the independent observations of Wolferth and Wood[1] and Wilson and his co-workers[2] were first reported in 1932. Differences of opinion and uncertainty still exist, however, concerning the most reliable and practicable method of utilizing precordial leads for clinical purposes, particularly with regard to the number of precordial positions that need to be explored and the proper location for the remote electrode. On the other hand, it is quite generally accepted at the present time that the traditional three limb leads[3] should be retained as the basic leads for clinical use, and that in conjunction with these one or more precordial leads should be employed. Although investigations dealing with "unipolar"[4] and "augmented unipolar"[5] limb leads, as well as with esophageal leads,[6] have aroused considerable interest during recent years, additional studies are needed to demonstrate how practical these special leads are for ordinary clinical use.

In 1938, the Committee of the American Heart Association for the Standardization of Precordial Leads[7, 8] described in detail the techniques for recording and agreed upon the terminology for identifying single and multiple precordial leads of various accepted types; but the Committee was unwilling at that time to decide on any standard procedure for the use of precordial leads in clinical practice. More recently this Committee[9] has expressed the opinion that a single precordial lead from the region of the cardiac apex, or from any other part of the precordium, is inadequate and has stated that three is the least number of precordial leads that can be regarded as satisfactory for general purposes. However, notwithstanding this and other recent developments[10-13] with regard to the superiority of multiple over single precordial leads, electrocardiograms which combine the three limb leads with only a single precordial lead are still used extensively. Probably by virtue of its originally demonstrated utility,[14, 15] the single precordial lead most commonly employed is an apical lead taken with the precordial electrode located at the outer border of the cardiac apex and with the remote electrode located on the left

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leg. The combination of Leads I, II, III, and IVF has been so widely used in clinical practice over the past decade that many physicians still erroneously believe that this particular series of leads constitutes the modern standard electrocardiogram, that the use of multiple precordial leads is a supplementary procedure for the more scientific study of selected cases, and that the need for multiple precordial leads can be anticipated in particular situations. In the light of recent experience and current informed opinion, these assumptions are not justified. One is forced to conclude, therefore, that the advantages of multiple rather than single chest leads and the necessity for their use in clinical practice have not been sufficiently emphasized.

Despite the reluctance of many cardiologists to adopt multiple precordial leads in ordinary clinical practice, among those who have studied precordial leads most fully,[9] there are no important disagreements regarding the superiority of multiple over single precordial leads for general purposes. On the other hand, the problem of the proper location for the remote electrode has become involved in the current discussion[16, 17] over the validity of the Einthoven equilateral triangle hypothesis[18, 19] that the human body acts, with respect to the three limb leads, essentially as a homogeneous volume conductor. Accordingly, there are differences of opinion on the best location for the remote electrode. The problem of the best location for the remote electrode needs further study and must be resolved before any single standard procedure for the routine use of precordial leads in clinical electrocardiography can be agreed upon. However, we have long felt[20] that the advantages of multiple over single precordial leads remain essentially valid, in most circumstances at least, for any of the currently recognized locations of the remote electrode. We feel very strongly, therefore, that it is the intrinsic superiority of multiple over single precordial leads that should be given special emphasis and wider attention, entirely apart from the uncertainties of the proper location for the remote electrode.

The study herein presented was planned to provide additional data regarding the practical advantages of employing multiple rather than single precordial leads, in conjunction with the three limb leads, in routine electrocardiographic diagnosis. For the purposes of this study, the IVF type of single precordial lead was employed because of its widespread popularity. The CR type of multiple precordial lead was used for comparison. A critical comparison of the CR, CL, CF, and V types of multiple precordial leads was not attempted and is not herein implied, since our particular interest was to provide a practical evaluation of multiple versus single precordial leads.

The present report deals, therefore, with the study of a large number of test subjects, some with and some without heart disease. On each subject, in correlation with the clinical findings, the electrocardiographic information furnished by Leads I, II, III, and IVF was compared with the information supplied by the three limb leads in conjunction with CR leads from the six recognized precordial positions.[8] From summaries and further analyses of these data, an effort was made to derive a statistical and inferential evalua-

tion of the relative merits of these two combinations of leads for use in practical clinical electrocardiography.

MATERIAL AND METHODS

Clinical and electrocardiographic examinations were made on each of 224 adult persons. These included an adequate number of normal controls and different examples of the commonly encountered forms of cardiac abnormality. No case was included on the basis of the comparative electrocardiographic findings per se.

Each of the 224 test subjects was thoroughly studied clinically to determine the presence or absence of cardiac abnormality and the etiological basis for heart disease, when present. The classification of the individuals studied, as determined by the clinical examination, is shown in Table I. Sixty-eight test subjects had no clinical evidence of heart disease and were utilized as normal controls, whereas 156 test subjects had definite clinical evidence of cardiac abnormality. In the latter group, 53 had hypertensive heart disease, 36 had experienced a recent myocardial infarction, 43 had coronary arteriosclerosis without indications of remote or recent myocardial infarction, 12 had chronic valvular heart disease of rheumatic or syphilitic origin, 5 had congenital cardiac lesions of a sort compatible with adult life, 4 had pulmonary disease with evidences of acute or chronic cor pulmonale, 2 had thyrotoxic cardiac disease, and 1 had a beri-beri heart.

TABLE I. CLINICAL CLASSIFICATIONS OF 224 INDIVIDUALS STUDIED

Total with no clinical evidences of heart disease (normal controls)	68
Hypertensive heart disease	53
Recent myocardial infarction	36
Arteriosclerotic heart disease	43
Valvular heart disease of rheumatic or syphilitic origin	12
Congenital cardiac lesions (adult type)	5
Pulmonary disease with acute or chronic cor pulmonale	4
Thyrotoxic heart disease	2
Beriberi heart disease	1
Total with definite clinical evidences of cardiac abnormality	156
Total individuals studied	224

One or more electrocardiograms were taken on each of the 224 persons studied. All tracings were made with the subjects in the reclining position. In every case Leads I, II, III, and IVF, and CR leads from the six recognized precordial positions[8] were recorded.

In analyzing the individual electrocardiograms, the three limb leads were interpreted as showing abnormality when significant cardiac arrhythmias were noted; when the P-R intervals or the QRS complexes were of greater duration than 0.20 and 0.10 second, respectively; when the QRS complexes showed low voltage in all three limb leads; when Q waves greater than 25 per cent of the amplitude of the R waves were present in Leads I or II; when broad S waves were noted in Leads I and II; when the S-T segments were displaced more than 1 mm. from the isoelectric line in either direction in any limb lead; when

T waves were diphasic, isoelectric, or inverted in Lead I or II; or when any combination of these findings was observed. Deviations of similar character in Lead III were regarded as abnormal only when significant associated changes could be detected in Lead I or II. The three limb leads were not regarded as abnormal when a benign arrhythmia (such as an occasional ectopic complex), or slight slurring of the QRS complexes, or slight to moderate axis deviation was the only feature observed.[22] Lead IVF and the six CR leads were interpreted as showing abnormality when significant arrhythmias were noted, or when the contours of the QRS complexes, the S-T segments, or the T waves in any one of these precordial leads, or the sequences of such contours in Leads CR_1 to CR_6, inclusive, deviated significantly from the normal forms as reported by Deeds and Barnes.[23] In judging whether definitive diagnostic patterns were shown by, or superior information could be derived from, different combinations of the precordial and limb leads, criteria for interpretation as set forth by Wilson et al.,[12, 17] Wood and Selzer,[10] Ashman and Hull,[24] Pardee,[25] and Katz[26] were used.

In the group of 68 test subjects with no clinical evidences of heart disease and the group of 156 test subjects with definite clinical evidences of cardiac abnormality, the number and percentages who showed electrocardiographic normality or abnormality in particular leads or combinations of leads were computed. In each case the record combining Leads I, II, III, and IVF was compared with the record which included the three limb leads and precordial leads CR_1 to CR_6, inclusive, in order to see which of these two combinations of leads revealed more definitive diagnostic patterns or supplied superior electrocardiographic information. Statistical summaries of these data were then attempted and were made when the comparisons appeared valid.

RESULTS

For the 68 subjects who were used as normal controls, the electrocardiographic findings in all leads of the ten-lead record were used in every case for this study. No comparative statistical summary concerning the demonstration of definitive diagnostic patterns by different combinations of the available leads could be derived from the records on these 68 control subjects, since in each case any combination of leads produced the definitive pattern of normality, in accordance with the criteria which we applied. However, the findings of normal contours and sequences of contours in the CR leads from the six precordial positions yielded a more complete definitive pattern of normal precordial potentials for each case than did the contours in the single Lead IVF. Consequently, for these 68 control subjects, the individual records consisting of the three limb leads in conjunction with the six CR leads did provide, inferentially at least, information on which to base the interpretation of electrocardiographic normality, which was superior to that given by the individual records which combined Leads I, II, III, and IVF.

For the 156 patients with definite clinical evidence of cardiac disease, the electrocardiographic findings yielded significant data when the ten-lead record of each case was analyzed. A summary of the numbers and percentages of

these 156 cardiac patients who showed abnormalities of one sort or another, when a particular lead or combination of leads was included for the analysis, is given in Table II. Fourteen (9 per cent) of these 156 patients showed electrocardiographic findings which were of entirely normal character for all leads of the ten-lead record. One hundred forty-two (91 per cent) of these cardiac patients were found to show definite abnormalities in one or more leads of this ten-lead record. In seven (4.5 per cent) of the 156 patients, the only electrocardiographic abnormality in any of the ten leads was an inversion of the T waves in Lead IVF. Analysis of the nine-lead record consisting of Leads I, II, III, and CR_1 to CR_6, inclusive, and of the six-lead record consisting of precordial leads CR_1 to CR_6, inclusive, revealed that both of these combinations showed electrocardiographic abnormalities in 135 (86.5 per cent) of the 156 cases. Likewise, the combination of Leads I, II, III, CR_1, CR_3, and CR_5, inclusive, showed abnormality in one or more leads for 135 (86.5 per cent) of these cardiac patients. The three limb leads were found to be abnormal for 119 (76.3 per cent) of the 156 patients with heart disease, whereas the four-lead record consisting of Leads I, II, III, and IVF showed abnormalities for 126 (80.7 per cent) of these cases. This last figure includes the seven cases in which inverted T waves in Lead IVF were the only abnormality observed in the ten-lead record. The numbers and percentages of these cardiac patients showing electrocardiographic abnormalities in leads from the individual precordial positions varied widely. Lead IVF was found to be abnormal for 91 (58.3 per cent) of the 156 cases, including the seven patients whose records showed T-wave negativity in Lead IVF as the only abnormality; whereas Lead CR_5 showed abnormality for 117 (75 per cent) and Lead CR_6 showed abnormality for 112 (71.8 per cent) of the cardiac patients. For each of the other CR leads, the number of patients showing electrocardiographic abnormality varied between 38 cases (24.3 per cent) for CR_1, to 66 cases (42.3 per cent) for CR_4 (Table II).

TABLE II. SUMMARY OF THE NUMBERS AND PERCENTAGES OF THE 156 PATIENTS WITH CLINICAL EVIDENCES OF HEART DISEASE WHO SHOWED ELECTROCARDIOGRAPHIC ABNORMALITIES WHEN PARTICULAR LEADS OR COMBINATIONS OF LEADS WERE UTILIZED FOR ANALYSIS

COMBINATION OF LEADS OR INDIVIDUAL LEADS ANALYZED	NUMBER OF PATIENTS SHOWING ABNORMALITY IN ONE OR MORE OF SUCH LEADS	PERCENTAGE OF TOTAL 156 PATIENTS
Leads I, II, III, IVF, CR_1 to CR_6	142	91.0
Leads, I, II, III, CR_1 to CR_6	135	86.5
Leads CR_1 to CR_6	135	86.5
Leads I, II, III, CR_1, CR_3, CR_5	135	86.5
Leads I, II, III	119	76.2
Leads I, II, III, IVF	126	80.7
Lead CR_1	38	24.3
Lead CR_2	48	30.8
Lead CR_3	53	35.2
Lead CR_4	56	42.3
Lead IVF	91	58.3
Lead CR_5	117	75.0
Lead CR_6	112	71.8

Our effort to determine, from the individual electrocardiograms on the 156 cardiac patients, the number of cases showing definitive diagnostic patterns by the different combinations of leads failed to yield a summary which we were willing to accept as valid in its implications. This failure resulted because in some of the cases difficulties were encountered in deciding or agreeing on whether the particular patterns shown by different combinations of the available leads could be considered definitive. For this same reason, there was disagreement about the number of cases in which the diagnosis indicated by a particular combination of leads could be made no more specific than "abnormal form of ventricular complex indicating myocardial damage." In this attempted analysis, however, it became impressively evident that the three limb leads constituted for practical purposes the indispensable basis for electrocardiographic diagnosis, and that the six CR leads, as well as the single Lead IVF, served largely to correct, modify, or enhance the diagnostic impressions derived from the three limb leads alone. The three limb leads were found to be definitely superior to the CR or IVF leads for indicating specifically the presence of a posterior or basal myocardial infarction.

When the individual electrocardiograms on the 156 cardiac patients were analyzed to determine the relative superiority of different combinations of the available leads for supplying practical electrocardiographic information, an apparently valid summary was derived by employing the three limb leads as the basic electrocardiogram and by determining the number of cases wherein added useful information was afforded by Lead IVF on the one hand, or by the six CR leads on the other. Of the 37 cases in which Leads I, II, and III were normal, in 14 cases Lead IVF and the six CR leads were likewise normal; in 7 additional cases Lead IVF showed inverted T waves as the only abnormality in the ten-lead records; whereas the six CR leads showed the only abnormalities and definitive diagnostic information in 16 cases. Of the 119 cases in which Leads I, II, and III were abnormal, in 93 cases the three limb leads yielded all the truly essential information that could be derived from the ten-lead record on each case; for none did Lead IVF yield any useful added information, whereas for 26 cases the six CR leads gave additional information. Therefore, of the total of 156 cases with clinical evidences of cardiac abnormality, all leads of the available ten-lead records were found to be normal in 14 cases (9 per cent), despite the definite evidences of cardiac abnormality indicated by the clinical examinations; in 93 cases (59.6 per cent) the three limb leads proved adequate to supply all the truly essential interpretative information that could be derived from the ten-lead records; in seven cases (4.5 per cent) Lead IVF alone of the available leads gave information indicating electrocardiographic abnormality; and in 42 cases (26.9 per cent) the six CR leads gave information regarding abnormalities and definitive diagnosis over and beyond that supplied by Leads I, II, III, and IVF.

With regard to the type of electrocardiographic information furnished by the different CR leads in the individual cases with clinical evidences of heart disease, we found in general that the CR_1 and CR_2 leads were particularly

useful for revealing abnormalities affecting preponderantly the right auricle or right ventricle, that the CR_5 and the CR_6 leads were particularly useful for revealing abnormalities affecting preponderantly the anterolateral aspects of the left ventricle, and that the CR_3 and the CR_4 leads were necessary to complete the definition of the precordial electrical field. More specifically, in one instance of syphilitic heart disease, Leads CR_1 and CR_2 were of value in detecting a cardiac arrhythmia of auricular origin (two-to-one auriculoventricular block), where, because of the blending of P and T waves, the presence of such an arrhythmia was not shown by the three limb leads, by Lead IVF, or by the other CR leads. In two patients with clinical evidences of long-standing mitral stenosis, in one instance of chronic cor pulmonale due to extensive pulmonary fibrosis, and in one case of interauricular septal defect, the CR_1 and CR_2 leads yielded evidence indicating right ventricular hypertrophy, and in two patients with coronary arteriosclerosis the presence of right bundle branch block was detected, when in each of these cases the findings noted in Leads I, II, III, and IVF were not regarded as definitely abnormal. Leads CR_2 and CR_4 in one instance revealed the presence of an acute anteroseptal myocardial infarction, the electrocardiographic diagnosis of which would have been missed had the tracing included only Leads I, II, III, and IVF, or, for that matter, the other CR leads. In eight additional cases, with hypertensive or arteriosclerotic heart disease, Leads CR_5 and CR_6 revealed electrocardiographic evidences of left ventricular hypertrophy, or of nonspecific myocardial abnormality (inverted T waves), which were not detected by Leads I, II, III, and IVF. Thus, for 16 (10 per cent) of the 156 patients with heart disease, the combination of Leads I, II, III, and IVF had to be interpreted in each as being within normal limits, whereas, from one or another of the multiple CR leads, the electrocardiographic findings permitted either a nonspecific or a definitive diagnosis of abnormality. Moreover, in four subjects with hypertensive heart disease, in 12 with acute myocardial infarction, in nine with arteriosclerotic heart disease, and in one case of patent ductus arteriosus, the electrocardiographic findings in Leads I, II, III, and IVF were abnormal but could not be considered clear-cut or specific; evidence of right or left ventricular hypertrophy, right or left bundle branch block, or the presence and extent of an acute anterior, anterolateral, or posterolateral myocardial infarction, were revealed only by the six CR leads. Thus, for an additional 26 (17 per cent) of the 156 patients with heart disease, compared to the findings shown by the three limb leads or by Lead IVF, the multiple CR leads gave superior information which permitted a more definitive electrocardiographic diagnosis to be made. It should be added that even for the 93 (60 per cent) of the 156 cases with heart disease wherein the three limb leads were regarded by us as being adequate to yield all the truly essential interpretative information that could be derived even from the ten-lead record, the six CR leads were in most instances definitely useful for corroborating and clarifying the character and extent of the electrocardiographic abnormality.

In the 156 cases with cardiac disease, 98 of the individual patients showed clinical evidences of rather severe congestive heart failure, and moderate or marked enlargement of the left ventricle was shown by the physical examination or by x-ray films or fluoroscopy. In more than one-third of these 98 cases, the electrocardiographic contours noted in Lead IVF suggested that this lead was not, in fact, directly reflecting the field of electrical activity resulting from the left ventricle. This seemed evident in some of these latter cases even though Lead IVF had been taken with the exploring electrode carefully located at the precordial point immediately lateral to the region of the cardiac apex. In all such instances, Leads CR_5 or CR_6, taken with reference to fixed anatomic locations on the chest, were found definitely superior to Lead IVF, because, by more clearly reflecting the field of electrical activity resulting from the enlarged left ventricle, they made possible a more accurate orientation and interpretation. Indeed, in this study the relatively poor showing obtained with Lead IVF seemed to result largely from the inherent difficulty of applying the precordial electrode at the true cardiac apex; even in instances where the three limb leads indicated quite clearly the presence of left ventricular hypertrophy, the contours noted for Lead IVF were often not abnormal. On the other hand Lead IVF did often show evidences of myocardial abnormality, or definitive diagnostic patterns of abnormality. However, the results obtained with Lead IVF in this study were relatively poor statistically because this lead often did not reveal evidences of abnormality affecting the right or left ventricle when either the three limb leads or the multiple CR leads, or both, showed such abnormality quite clearly.

In comparing the findings noted for the combination of Leads CR_1, CR_3, and CR_5 with the information furnished by the combination of Leads CR_1 to CR_6, inclusive, we found that each of these combinations showed electrocardiographic abnormalities in the same number of patients with heart disease (see Table II). On the other hand, for the entire group of cases with heart disease, it was not possible to select any combination of three CR leads which would permit as reliable and definitive an evaluation of the precordial potential variations as was derived from the use of all six CR leads. This is readily understandable when one considers the variability of the size and position of the heart in the chest, as well as the variability in the type of electrocardiographic contours noted from the different precordial positions.

DISCUSSION

The results of this study are in keeping with the previously reported findings of others[10-12] and lend support to the indications for the use of precordial leads. In addition, they provide, at least in part, a statistical comparison of the information derived from the three limb leads alone, and from the three limb leads in conjunction with single or multiple precordial leads. It should be emphasized that for 60 per cent of the cases with cardiac disease the three limb leads proved adequate to supply all the truly essential interpretative information that could be derived from the ten-lead records herein employed.

It might be inferred as well, though with some reservation, that in the cases without clinical evidence of cardiac abnormality the three limb leads were adequate to indicate electrocardiographic normality. These results, therefore, tend to explain the great reluctance of many cardiologists to add any material number of additional leads to the traditional limb leads record and strongly support the view that the three limb leads must remain the basic and indispensable leads for practical clinical electrocardiography at the present time. On the other hand, in this study the six precordial leads added appreciable electrocardiographic information. In 27 per cent of the patients with clinical evidences of heart disease, the six CR leads gave additional information of value regarding abnormalities, and/or definitive diagnosis over and beyond that supplied by Leads I, II, III, and IVF. In the individuals without clinical evidences of cardiac abnormality, moreover, the multiple CR leads lent added assurance to the diagnosis of electrocardiographic normality, and it was felt in the majority of these cases that the relative size and position of the heart in the chest could be more accurately inferred from the six CR leads.

In our material, however, it was observed that the single precordial Lead IVF, despite its current widespread popularity, added relatively little information to that indicated or suggested by the three limb leads alone. Although in seven of the 156 patients with heart disease T-wave negativity in Lead IVF was the only observed abnormality in the ten-lead record, this abnormality obviously resulted from a difference in the character of the electrical potentials occurring at the left leg and at the right arm, since all the CR leads were normal in these seven cases. Therefore, the exact significance of this finding, in terms of its detecting intrinsic cardiac abnormality rather than the effects of cardiac position,[27] or of its indicating the superiority of CF- over the CR-type of precordial leads, is uncertain and remains for other studies to determine. Additional objections to Lead IVF as the only precordial lead were also noted in this study. One of the most potent is the difficulty of placing the precordial electrode just beyond the region of the true cardiac apex in certain patients, especially those with enlarged left ventricles. Improper placing of this electrode may actually vitiate whatever value a single precordial lead has for electrocardiographic diagnosis. Moreover, our observations in this study suggest that, particularly where left ventricular hypertrophy is present, the field of electrical potential preponderantly reflecting left ventricular activity may in some instances be located farther to the left than the anatomic apical area.

In this study the electrocardiographic record combining the three limb leads with precordial leads CR_1, CR_3, and CR_5 revealed abnormalities in the same number of patients with heart disease as did the record combining the three limb leads with precordial leads CR_1 to CR_6, inclusive. The former combination did not reveal with the same certainty the character of the precordial electrical field, and in a fair number of instances would have resulted in an incorrect or less definitive interpretation than the latter. Objective evidence to support this view was not derived because we were unwilling to

compare statistically merely suggestive with more clear-cut electrocardiographic findings. On the other hand, the combination of precordial leads CR_1 to CR_6, inclusive (without limb leads), also revealed abnormalities in the same number of cases with heart disease as were revealed by the combination of the three limb leads with the six CR leads; but, in the entire group of cases with heart disease, the former combination certainly did not yield the same amount of definitive diagnostic information as did the latter. Because of the variability of the findings indicated by the individual CR leads for the entire group of cases, we believe that it is impossible to employ with any reasonable success less than the six recognized precordial leads since that would require an anticipatory knowledge of the probable location and type of the abnormality to be found. Moreover, in this study we observed that any attempt to reduce the number of precordial leads, even to as few as three, often resulted in loss of the fundamental advantage in the use of precordial leads which is derived from the exploration of the entire precordium.

The objection has been raised that, in comparison with the additional information derived, the use of six rather than a single precordial lead in conjunction with the three limb leads, entails for practical clinical purposes too much additional effort in recording and interpreting the resulting electrocardiogram. From our results in the present study, we are not in sympathy with such objections. Rather, we believe that precordial leads have definite practical value for clinical use, that a single precordial lead is woefully inadequate for proper orientation and interpretation of precordial electrical potentials, and that whenever complete electrocardiographic information is desired, one cannot in the present state of knowledge afford to do less than combine the three limb leads with a record which explores the entire precordium, using leads from the six recognized precordial positions.

SUMMARY AND CONCLUSION

1. Clinical and electrocardiographic examinations were made on 224 individuals. Judged by the clinical findings, sixty-eight were found to be free of heart disease and 156 had definite evidences of cardiac abnormality.

2. On each test subject, electrocardiograms were utilized which included Leads I, II, III, and IVF and CR leads from the six recognized precordial positions and which were analyzed statistically and inferentially to determine the comparative value of multiple versus single precordial leads for use in conjunction with the three limb leads for practical clinical electrocardiography.

3. For the entire 224 cases, the three limb leads were found essential as the basic leads for the electrocardiographic study, and were found to be of fundamental value in the electrocardiographic interpretations.

4. For the 68 subjects with normal hearts, the individual records consisting of the three limb leads in conjunction with the six CR leads provided information on which to base the interpretation of electrocardiographic normality which was superior to that provided by the individual records which combined Leads I, II, III, and IVF.

5. For the 156 cases with clinical evidences of cardiac abnormality, the six CR leads in conjunction with the three limb leads were found definitely superior to Leads I, II, III, and IVF for providing information both as to abnormality and type of abnormality present. Statistical data to support this view are given.

6. It is concluded that precordial leads should be employed in combination with the three limb leads for practical clinical purposes, and that the most reliable and complete electrocardiographic information is afforded when leads from the six precordial positions are routinely used for this purpose.

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Clinical Reports

ABNORMAL ELECTROCARDIOGRAM FOLLOWING RECOVERY FROM PAROXYSMAL TACHYCARDIA

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THE case described below presents an interesting and rather unusual electrocardiogram following recovery from paroxysms of tachycardia. This consists of the spreading out of the T waves to produce a prolonged Q-T interval, associated with inversion of the T waves and depression of the corresponding S-T segments. Similar cases have been described in the literature, but they seem to be quite rare.

Graybiel and White[1] reported a case of ventricular tachycardia in 1934 in which the electrocardiogram taken after recovery showed inversion of the T wave in Leads II and III. There was a gradual return to normal within a few months. They found no similar electrocardiogram in their records. This patient had no apparent organic heart disease. While the Q-T interval was not mentioned specifically, the tracings show it to be about 0.46 second. Six weeks later the interval had been reduced to 0.40 second. (This figure is not entirely accurate since the 0.04 second marker line does not appear on the record.)

Schulten[2] reported one case in which the electrocardiogram after recovery from ventricular tachycardia showed a prolonged Q-T interval, with inversion of the T waves in all leads. During the following four weeks, first Lead I, then, successively, Leads II and III of the electrocardiogram gradually returned to normal.

Cossio and his co-workers[3] reported four cases. Three of these cases showed depressed S-T segments and negative T waves in Leads II and III; the other showed negative T waves in Leads I and II. At autopsy one case showed cardiac dilatation, but there was no involvement of the coronary vascular system and no focal necrobiosis. The changes were believed to be due to enlargement of the heart or right ventricular strain and not to the presence of a real coronary insufficiency. Campbell[4] agrees that such electrocardiographic changes do not indicate organic disease but are a completely reversible process indicating some degree of exhaustion or strain of the heart muscle.

Geiger[5] recently reported a case in which this type of electrocardiogram was encountered after recovery from supraventricular tachycardia. The patient had had two attacks ten years apart. No clinical evidence of heart disease

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could be demonstrated after recovery, and the author warns of the danger of interpreting the changes in the electrocardiogram seen after recovery as being due to coronary thrombosis.

CASE REPORT

First Admission.—A 19-year-old white youth was admitted to the hospital on July 3, 1942, because of palpitation of the heart. The attack had started suddenly, without apparent cause.

He gave a history of similar attacks in the past, the first having occurred at the age of 12 years. This attack subsided spontaneously after a few hours. Two years later, during a basketball game, he had another attack. During the next five years he had frequent attacks, usually following exertion, but sometimes occurring without apparent cause. There was no history of previous illness nor of any rheumatic manifestations. Except for these attacks, he had been in good health and was a normal vigorous boy. He smoked about three packages of cigarettes daily.

On examination the patient did not seem acutely ill. The respirations were 28 per minute but not labored. There was no cyanosis. The arteries of the neck were seen to be pulsating rapidly, and the veins appeared slightly full. The apical impulse of the heart was visible in the sixth intercostal space, 1 cm. outside the midclavicular line. There was no palpable thrill, nor was there an audible murmur. The heart sounds were very rapid and had a "tic-tac" quality. The heart rate was about 200 per minute. The lungs were entirely clear. The liver extended 2 fingerbreadths below the right costal margin and was not tender. There was no edema. The temperature was normal. Urinalysis showed 1 plus albumin.

An electrocardiogram taken on admission showed paroxysmal tachycardia,* with a ventricular rate of 210 per minute (Fig. 1, *A*). One hour after the administration of 6 grains of quinidine sulfate by mouth, the heart rate had decreased to 120. Due to an error, 30 additional grains of quinidine sulfate were given in the next six hours. An electrocardiogram taken at this time (Fig. 1, *B*) showed regular sinus rhythm with very peculiar T waves. Besides being inverted in Leads II and III, they were spread out so that the Q-T interval was 0.48 second, as compared with the commonly accepted normal maximum of 0.39 second. There was also slight depression of the S-T segments in these leads, and the P waves were very prominent.

Examination of the heart after sinus rhythm had been restored showed the apex beat outside the mid-clavicular line. A harsh systolic murmur, loudest in the fourth intercostal space to the left of the sternum, was heard over the entire precordium.

Because he felt well, the patient insisted on leaving the hospital. Four days later he returned for another electrocardiogram (Fig. 1, *C*). There was still inversion of the T waves and depression of the S-T segments in Leads II and III, but the Q-T interval had decreased to 0.36 second, which is well within normal limits. In the chest lead the T wave had become inverted and the inversion of the P wave had disappeared. In Leads II and III the P wave was still prominent.

Second Admission.—Before a fourth electrocardiogram could be taken, the patient developed another paroxysm of tachycardia. This attack had started during a wrestling bout. The physical findings were the same as on his original admission. The blood pressure was 90/70, and the pulse rate was about 200 per minute. The electrocardiogram taken on readmission (Fig. 2, *A*) again showed paroxysmal tachycardia. The urinalysis and blood count were normal. The mouth temperature was 99.6° F. Six grains of quinidine sulfate were given. Two hours later the patient began to sweat, and he vomited several times. His blood pressure was 80/60. Four hours after the medication the cardiac rhythm became normal and he was placed on a maintenance dose of 3 grains of quinidine sulfate three times a

*Although the tachycardia appears to be ventricular in origin, this cannot be positively established. Since the type of tachycardia has no bearing on the findings that are being emphasized, no further attempt will be made to identify the origin of the tachycardia.

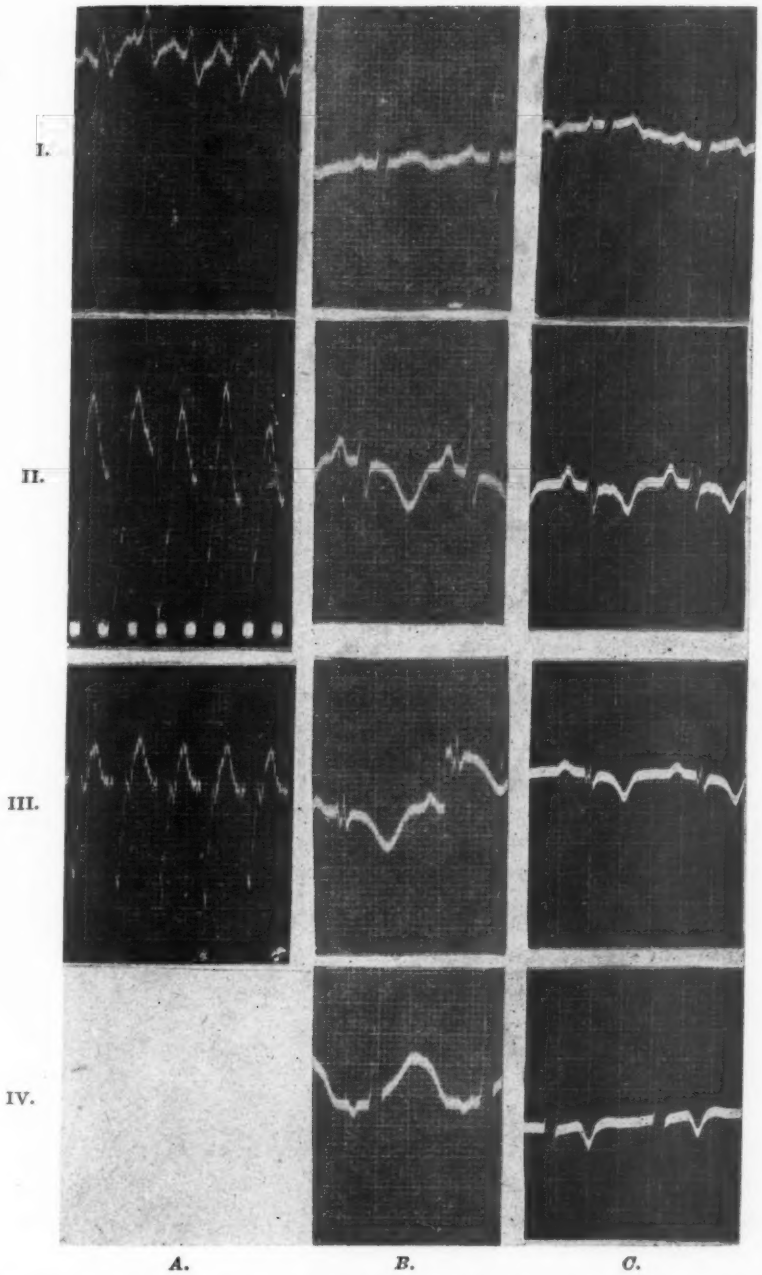

Fig. 1.—*A*, Tracing taken on first admission, July 3, 1942, shows paroxysmal tachycardia. The chest lead is missing. *B*, Tracing taken after restoration of sinus rhythm, July 4, 1942, showing peculiar T waves and prolonged Q-T interval. *C*, Tracing taken July 8, 1942, showing normal Q-T interval; T waves are still inverted.

day. A tracing made the following day (Fig. 2, *B*) was similar to the one taken after cessation of tachycardia on his first admission. (A technical error produced an inverted Lead IVF.) The Q-T interval was again 0.48 second, as it was in Fig. 1, *B*. A teleroentgenogram showed moderate enlargement of the heart, especially pronounced in the apical region.

Again the patient insisted on leaving the hospital. He was advised to remain under medical supervision.

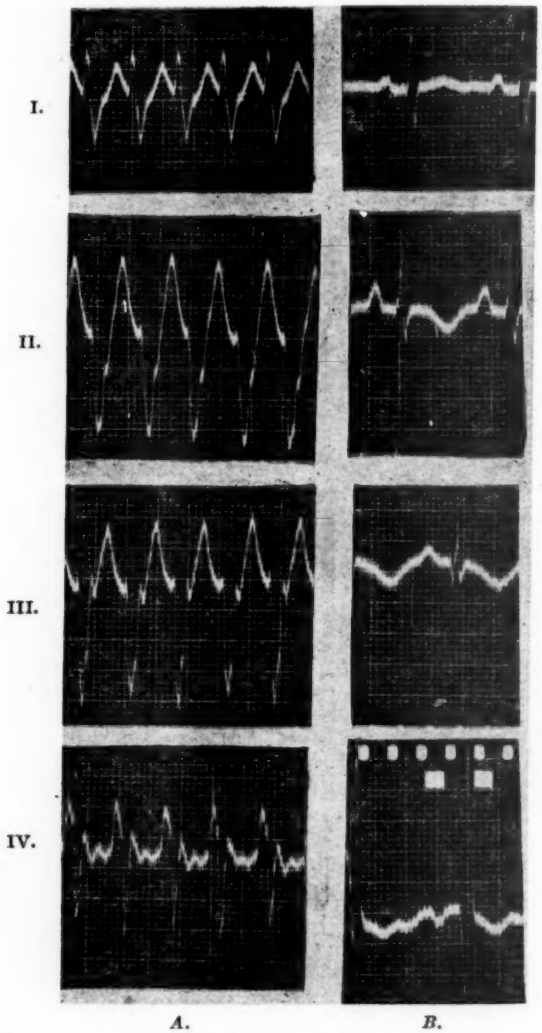

Fig. 2.—*A*, Tracing taken on second admission, July 12, 1942, identical with Fig. 1, *A*. *B*, Tracing taken July 13, 1942, after restoration of sinus rhythm, identical with tracing 1, *B*.

Third Admission.—He was readmitted on Aug. 3, 1942, with another paroxysm of tachycardia which had begun while he was at rest. Eighteen grains of quinidine sulfate administered within a period of eight hours restored the cardiac rhythm to normal. He had not been under a doctor's care nor had he taken any medicine since his last dismissal. He insisted on leaving the hospital before any observations could be made, and shortly thereafter he left the city.

DISCUSSION

The two interesting changes in the electrocardiogram after recovery from tachycardia are a prolonged Q-T interval and an inversion of the T waves. In some reported cases the T waves in all the limb leads were inverted; in others only the T waves of Leads I and II or II and III were inverted. The present case falls into the latter category.

White and Mudd[6] established a normal range for electrical systole as determined by the Q-T interval. They found that this interval depends on the heart rate and is more prolonged at lower rates. For instance, at a heart rate of 160, the Q-T interval varied between 0.21 and 0.24 second; while at a heart rate of 60, the variation was from 0.26 to 0.44 second. These are extreme ranges and most of the cases fell near the mid-point, averaging about 0.34 second with slow rates. They also found prolongation of the Q-T interval in association with such electrocardiographic abnormalities as bundle branch block, paroxysmal tachycardia of both the auricular and the ventricular type, and ventricular premature contractions. Among the extracardiac factors which may lengthen electrical systole are hypocalcemia[6, 7] and hypopotassemia.[8]

Inverted T waves are seen in many conditions; no attempt will be made to enumerate them all. A common condition associated with T-wave inversion is myocardial infarction, and this may confuse the physician when confronted by a patient who develops a sudden ectopic rhythm, usually associated with precordial distress and dyspnea. I believe that the electrocardiogram of recovery from tachycardia is not typical of the electrocardiogram of myocardial infarction, and if the characteristics are kept in mind, confusion will be avoided. It is unfortunate that more prolonged follow-up in this case was not possible. It would have been interesting to see whether or not the T-wave inversions reverted to normal as they have done in other reported cases. It must be remembered, however, that in many of these cases the patients had normal hearts, while the patient here reported probably had a congenital patent interventricular septum, and it is possible that Leads II and III of his normal electrocardiogram would show inverted T waves indicative of right ventricular enlargement, even though there was no right axis deviation.

SUMMARY

A case showing an abnormal electrocardiogram following recovery from paroxysmal tachycardia is reported. The abnormalities consist of a prolongation of the Q-T interval and inversion of some or all of the T waves, with depression of the associated S-T segments. It should be recognized that such changes can be the result of paroxysmal tachycardia and are not necessarily an indication of the presence of serious organic disease. A brief review of the relevant literature is included.

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SUBACUTE BACTERIAL ENDOCARDITIS SUCCESSFULLY TREATED WITH PENICILLIN

Report of a Case

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F. H. J., a 31-year-old white man, was incarcerated in the United States Northeastern Penitentiary, Lewisburg, Pa., on Oct. 4, 1944. He was assigned to the work of handling steel on the night shift of prison industries. He worked steadily at this job for slightly more than three months. On the evening of Jan. 13, 1945, he reported to the prison hospital, complaining of shortness of breath and palpitation of three days' duration. He stated that he had "low blood pressure" and that six months previously an Army induction board had classified him 4F because of this condition. Further questioning revealed that he had had acute rheumatic fever at the age of 11 and again at the age of 16 years. At the age of 27 years a fainting spell led to several weeks' hospitalization. He was told by his attending physician at that time that he had suffered a heart attack.

The patient was therefore admitted to the prison hospital for study. Upon admission he appeared well developed and well nourished and was in no acute distress. His weight was 182 pounds. He was ambulatory and well oriented. The temperature was 98° F., the pulse was 100, and the respirations were 20 per minute. The blood pressure was 134/50. The skin was sallow. There was no lymphadenopathy. The eyes showed an old chorioiditis. There was extensive gingivitis and dental caries. Examination of the heart revealed a forceful apex thrust in the fifth intercostal space 12 cm. to the left of the midline; there were no palpable thrills; the rate was 100, with a regular rhythm. The apical first sound was accentuated and roughened, followed immediately by a short high-pitched systolic murmur. The aortic second sound was muffled and partially obscured by a to-and-fro systolic and diastolic murmur which was transmitted into the neck vessels. There was no ankle edema, no hepatic engorgement, no distention of the jugular veins, and no râles in the lung bases. Duroziez's sign was equivocal. An electrocardiogram showed widening of the QRS in all leads, inverted P_4, deep Q_3, inverted T_1 and T_2, elevated RS-T_3, depressed RS-T_4, and left axis deviation. A teleroentgenogram of the chest showed the heart to be at the upper limit of normal size, with slight prominence of the left ventricle.

The patient was observed for two weeks. During this time he was ambulatory, slept without difficulty on one pillow, remained entirely afebrile, and had no complaints. On Jan. 31, 1945, when arrangements with the prison administration for sedentary occupation had been completed, he was discharged. The diagnosis on discharge was inactive rheumatic heart disease with aortic stenosis and insufficiency and possible early mitral insufficiency.

Nine days later, the patient again reported to the hospital complaining of a cold and sore throat which had been present for the previous forty-eight hours. Fever and pains in the hips, knees, ankles, and wrists had existed for twenty-four hours. Examination revealed: temperature, 100; pulse rate, 100; respiration, 24; blood pressure, 134/50. The skin was warm and flushed, but there were no petechiae. The cervical lymph nodes were shotty and tender. The pharyngeal mucous membranes were injected. The left ankle and right hip were tender to touch but were not warm, reddened, or swollen. The cardiac findings were the same as had been noted previously. The blood count showed: red blood cells, 5,390,000; hemoglobin, 12.6 Gm.; white blood cells, 8,250; polys, 64 per cent, lymph-

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ocytes, 21 per cent; monocytes, 13 per cent; eosinophiles, 2 per cent. The sedimentation rate (Wintrobe) was 31 mm. per hour. The urinalysis was negative. The patient was admitted to the hospital with a tentative diagnosis of an acute exacerbation of rheumatic fever. He was put to bed and given full doses of sodium salicylate, which relieved the joint symptoms. After ten days of symptomatic therapy, however, the fever still persisted, averaging 100.4° F. The pulse consistently remained over 100. A blood culture taken on the thirteenth hospital day, showed on the eighteenth day a pure culture of streptococcus viridans with eight colonies per cubic centimeter. A second culture, taken on the twentieth day, was again positive for streptococcus viridans. Three additional cultures taken prior to the administration of penicillin were also positive.

On the twenty-fifth hospital day, cardiac changes were first evident; a diastolic thrill and a low-pitched rumbling diastolic murmur were detected at the apex; the apical systolic murmur had become longer; the blood pressure was 134/10.

On the thirty-second hospital day the patient developed in his left conjunctiva his first and only petechia. The following day he suddenly developed severe precordial pain radiating to the left axilla; his left arm suddenly became numb and partially paralyzed. Use of the arm returned slowly over a ten-day period.

Penicillin therapy was started on the thirty-sixth day. In vitro sensitivity tests were made at the beginning of penicillin therapy in the following manner:

A loopful of a forty-eight-hour broth culture of the patient's blood was inoculated into each of several flasks of brain-heart infusion broth containing penicillin in concentrations ranging from 0.0005 unit per cubic centimeter to 0.5 Oxford unit per cubic centimeter. After a seventy-two-hour incubation period it was found that there was complete inhibition of growth of the organisms in those flasks whose penicillin concentration was 0.05 unit per cubic centimeter or greater, while growth was noted in all flasks whose penicillin concentration was lower than 0.05 unit per cubic centimeter.

During the first ninety-six hours, 770,000 units of penicillin were given by continuous intravenous drip. Each 100,000 units were dissolved in 1 L. of 5 per cent dextrose in distilled water. Because of the severe local reaction, however, the penicillin was administered intramuscularly, 30,000 units being given every three hours for three days. The dosage was then lowered to 15,000 units every three hours and was maintained at this rate for three days but, because of a slight afternoon temperature rise with the smaller dose, was then raised to 20,000 units every three hours. This dosage was continued for eight days and then increased to 30,000 units every three hours for five and one-half days. Although 3,440,000 units were given intramuscularly, the patient tolerated the injections extremely well. A concentration of 10,000 units per cubic centimeter was employed. When treatment was terminated, on the fifty-eighth day, a total of 4,210,000 units had been given continuously over a twenty-three and one-half day period.

After six days of treatment the teeth were x-rayed. An abscess was found at the root of the lower right first bicuspid. The tooth was extracted, but unfortunately no culture was taken from the abscess.

Blood cultures which, before treatment, had been persistently positive for *Streptococcus viridans,* became sterile twenty-four hours after the initiation of treatment. Cultures taken every seventy-two hours during the administration of penicillin and at weekly intervals since, have been sterile to date. Seven weeks have elapsed since treatment was discontinued.

The temperature, which had averaged 100.4° F. prior to the initiation of penicillin therapy, fell rapidly to normal and remained normal except for afternoon rises of less than 1° F. After nine days of therapy the patient became completely afebrile and has remained so. The pulse likewise slowed from between 100 and 110 to between 80 and 90, and remained at this rate even when the patient became ambulatory. The diastolic blood pressure, which had fallen from its original level of 50 mm. to 10 mm., rose gradually and at the termination of therapy stood again at 50 millimeters. Likewise, the diastolic apical bruit which developed during the first part of hospitalization diminished in intensity con-

siderably during and after treatment. It seems most likely that this represented a true Flint's murmur, particularly since a very recent teleroentgenogram of the heart showed no change in size or shape of the left auricle as compared with the previous picture that would indicate the development of mitral stenosis. The patient's weight, which had fallen from 182 pounds on admission to 157 pounds, was 190 pounds at last report. During therapy the only change in the blood picture was a transient eosinophilia of 5 to 9 per cent. There was never any profound anemia or leucocytosis. The urine showed no abnormalities at any time. The sedimentation rate remained between 31 and 38 mm. per hour during treatment but had fallen to 9 mm. per hour seven weeks later.

Although at least six months must elapse before it can be stated with finality that this patient has been clinically and bacteriologically cured of his disease, his blood has been sterile for ten weeks; no treatment has been given for seven weeks. While the prognosis must still be guarded, the outlook for complete bacteriologic cure in this case is good. Despite our enthusiasm over a new and apparently efficacious drug for a hitherto fatal disease, we must remember that this patient has recovered with further damage to an already deformed heart. This will not only limit his physical activity but also increase the likelihood of reinfection.

ADDENDUM

At the time of his discharge from prison, in March, 1946, the patient was still bacteriologically negative.

Abstracts and Reviews

Selected Abstracts

Warren, J. V., Stead, E. A., Jr., and Brannon, E. S.: The Cardiac Output in Man: A Study of Some of the Errors in the Method of Right Heart Catheterization, Am. J. Physiol. **145:** 458 (Feb.) 1946.

This paper is an appraisal of certain features of the catheter technique of cardiac output determination as based on the authors' experience with the method in over 500 subjects. Variation between the oxygen content of paired consecutive samples of arterial blood did not exceed 0.4 volume per cent and in 77 per cent of the determinations was 0.2 volume per cent or less. In 111 instances in which comparative determinations were made of blood from the right atrium, 78 per cent varied no more than 0.4 volume per cent, but the remainder varied as much as 2.3 volumes per cent. In 25 instances of similar determinations on ventricular blood, 80 per cent varied no more than 0.4 volume per cent, and the remainder varied as much as 1.8 volumes per cent. Comparison of the oxygen content of atrial and ventricular blood samples in 19 patients showed variation of 0.4 volume per cent or less in 11 patients, 1 volume per cent or less in 11 patients and 1.2 volumes per cent in two patients. Check of 42 duplicate samples of expired air was within 10 per cent in 31 instances and as much as 20 per cent in the remaining 11 instances. It appears possible that some of the variation between consecutive samples of ventricular blood are due to changes in cardiac output rather than technical errors. The errors in the values for oxygen consumption seem partly technical and partly real. It is concluded that the catheter method is more accurate in situations in which the arteriovenous oxygen difference is great. The errors involved seem to be random rather than systematic. Results obtained with this method are more valid when groups rather than individuals are studied, as the inaccuracies in individual values for cardiac output are occasionally large. LAPLACE.

Elbel, E. R., and Green, E. L.: Pulse Reaction to Performing Step-Up Exercise on Benches of Different Heights. Am. J. Physiol. **145:** 521 (Feb.) 1946.

The present study was conducted to determine whether variation in the height of the bench or stool significantly affects the pulse reaction of normal subjects to the step-up exercise. The subjects were seventy-two healthy aviation students. Each subject was tested ten times, twice on each of five benches which were 12, 14, 16, 18, and 20 inches in height. Two periods of exercise were used for each bench, one for thirty seconds and one for sixty seconds. The exercise was performed at a rate of 24 steps per minute.

The pulse rates for the thirty seconds immediately after exercise depended upon the height of the bench and the duration of the exercise. After the thirty-second exercise, the average increment was 3.7 beats per minute greater for each additional 2-inch increase in height of the bench; after the sixty-second exercise, the average increment was 5.6 beats per minute. The pulse rates taken one minute after exercise were practically the same for the various heights of the benches and durations of exercise. LAPLACE.

Nini, Mehreb, and Saadeh: Buerger's Disease. Rev. méd. franç. du Moyen-Orient **3:** 391 (May) 1945.

Four cases of Buerger's disease are presented, together with a discussion of the symptomatology, diagnosis, and treatment. Therapy of one of the reported cases, which appeared responsible for conspicuous clinical improvement, was the use of antirabies vaccine.

This treatment was discovered by chance when a patient who had Buerger's disease was bitten and attended the local Institute daily for vaccine therapy. After several injections he noted that he no longer had to ride but could easily walk to the Institute, a distance of 1 km., without pain. Repetition of the treatment in additional cases has given good results. The favorable effect of the antirabies toxin is considered comparable with that of cobra toxin.

LAPLACE.

Blair, H. A., and Wedd, A. M.: The Action of Cardiac Ejection on Venous Return. Am. J. Physiol. **145**: 528 (Feb.) 1946.

The authors discuss their views regarding the mechanical relationships between cardiac ejection, lung air pressure, chest wall movements, and venous return. Observations on which their conclusions are based included synchronous recording of the electrocardiogram and volume curves of the neck, chest, and upper abdomen. It is stated that the excess of arterial outflow over venous inflow to the chest during systole tends to create a partial vacuum of about 15 mm. Hg in the lungs, but collapse of the chest wall permits only about 0.5 mm. Hg of this pressure to be realized. This partial vacuum is not nearly so important in assisting venous return as the negative intrapleural pressure. Cardiac failure may be expected to increase the promotion of venous return by causing the accumulation of blood in the lungs, which decreases lung volume and diminishes lung movement. In mitral stenosis, even in the absence of failure, the venous return to the chest frequently appears to exceed the arterial outflow during systole. This is indicated by the finding that in these cases the chest may expand during systole rather than collapse.

LAPLACE.

Nahum, L. H., and Hoff, H. E.: The Configuration of Epicardial and Endocardial Extrasystoles in the Chest Leads. Am. J. Physiol. **145**: 615 (Feb.), 1946.

Extrasystoles were recorded from the epicardial and endocardial surfaces of the right and left ventricles of dogs. Four leads were recorded: transthoracic, IVF, IVR, and the central terminal lead of Wilson. It was found that when the stimulating electrodes were aligned with the transthoracic leads or were immediately subjacent to the exploring electrode in the chest leads, there was no difference between epicardial and endocardial extrasystoles, the initial deflections of both showing a simple QS complex. When the stimulating electrodes were placed otherwise, the extrasystoles were of differing patterns according to their source.

It is inferred that the electrocardiogram as recorded by limb and chest leads does not reveal the existence of currents associated with the conduction of excitation from the endocardium and epicardium.

LAPLACE.

Evans, W. F., and Graybiel, A.: Electrographic Evidence of Cardiac Complications in Infectious Mononucleosis. Am. J. M. Sc. **211**: 220, 1946.

The authors studied 100 patients with infectious mononucleosis and concluded that four of the 100 patients had some type of cardiac complication associated with the disease. This opinion was based chiefly on the presence of electrocardiographic changes. The principal changes were progressive lowering of the height of the QRS complexes and the T waves. In two of the four patients the T waves became actually inverted. These changes gradually disappeared and the tracings ultimately became normal. In addition to the electrocardiographic evidence of cardiac involvement, there were some confirmatory clinical evidences in three patients, although the clinical signs were not striking. The heart rate was slow in proportion to the temperature in all three patients. In one patient a pericardial friction rub was present and in another there was some cardiac enlargement. None of the patients had cardiac failure. The presence of a friction rub in one case, as well as the type and course of the electrocardiographic changes led the authors to suspect that the pericardium rather than the myocardium was the chief site of involvement. A fifth patient, who had massive pericardial effusion for which no etiology other than infectious mononucleosis could be found, lent some support to this view.

The authors did not feel that there was any likelihood that rheumatic fever was responsible for the findings in these four patients. However, three of the four patients had an erythematous rash and joint pains. This suggests that the diagnosis of rheumatic fever may occasionally have to be eliminated in making a diagnosis of infectious mononucleosis.

McMILLAN.

Ward, D. E., Jr., and Harrell, George T.: The Effect of Salicylate Therapy on the Weltmann Serum Coagulation Reaction and Its Use as a Prognostic Test in Rheumatic Fever. Am. J. M. Sc. **211**: 157 (Feb.), 1946.

In addition to the leucocyte count, two laboratory tests are available for the estimation of the degree of activity and the prognosis of rheumatic fever: the sedimentation rate and the Weltmann reaction which is based upon the fact that calcium chloride coagulates blood serum. Since there is evidence that the sedimentation rate may be altered by salicylate therapy, the authors have studied the Weltmann reaction to determine whether it likewise is influenced by salicylates, and also to determine its sensitivity and usefulness in comparison with the sedimentation rate.

In normal serum the Weltmann coagulation band is always 6. While salicylate in concentrations much higher than those ever obtained in human subjects did shift the band to 7, the reaction was not affected by salicylate in anything like the concentration obtained under clinical conditions.

In the presence of active inflammatory change, the sedimentation rate increases and the coagulation band becomes lower. As activity lessens, the sedimentation rate lowers and the coagulation band shifts to the right toward the normal of 6. In untreated patients, the two reactions are generally but not always parallel. However, since the sedimentation rate is altered by salicylate, while the Weltmann reaction is not, the authors feel that the Weltmann reaction is a more reliable measure of activity.

McMILLAN.

Lequime, J., van Heerswynghels, J., and Herlant, M.: Contribution to the Study of Congenital Dilatation of the Pulmonary Artery. Arch. d. mal. du cœur **37**: 7 (Jan.-Feb.), 1944.

Clinical observations and autopsy findings are reported in a case of a woman, aged 32 years, who presented the syndrome of large pulmonary artery and small aorta. The patient had been breathless on effort since infancy and had been cyanotic since the age of 6 years. Essential features of the physical examination were cyanosis, clubbing of the fingers, a systolic murmur at the cardiac apex, and a faint diastolic murmur at the sternal border in the third left intercostal space. Radiography revealed a small aortic knob, very large pulmonary conus, and enlargement of the left ventricle. The electrocardiogram showed right bundle branch block. On postmortem examination, the right and left ventricles and the right auricle were hypertrophied and dilated, the pulmonary artery was greatly widened, and the aorta was narrowed along its entire course. An opening in the interventricular septum was present, having the diameter of 1 fingerbreadth, and situated just below the mitral and tricuspid valves. A second opening was present in the interauricular septum having a diameter of 1 centimeter.

Studies prior to the onset of cardiac failure had shown that the arterial blood had an oxygen saturation of only 74 per cent. From this it was calculated that 37 per cent of the venous blood by-passed the lungs by way of the shunt. The presence of the veno-arterial shunt was also manifested by an arm-to-tongue circulation time of 12 seconds. It is pointed out that the veno-arterial shunt is a critical handicap, the absence of which permits the patient to tolerate much better the aortic and pulmonary defects.

LAPLACE.

Conte, W. R., McCammon, C. S., and Christie, A.: Congenital Defects Following Maternal Rubella. Am. J. Dis. Child. **70**: 301 (Nov.-Dec.), 1945.

Evidence is presented which suggests that infection with rubella predisposes toward development of congenital anomalies. To date, 136 cases of congenital anomalies have been

reported, in which a definite history of a virus infection in the mothers during pregnancy has been obtained. In all but two of these cases, the offending virus disease was rubella. In all but five cases, the rubella occurred before the third month of pregnancy.

Of the 136 patients, 80 per cent had unilateral or bilateral cataracts; 62 per cent were mentally deficient; 57 per cent had heart disease, and 54 per cent had a combination of cataracts and heart disease. It is difficult to evaluate the significance of these reported cases because it is not known how often malformations occur without being the result of virus infection.

One hundred and twenty cases of congenital anomalies studied by the authors revealed five cases with a history of rubella occurring during pregnancy. This incidence of 4.2 per cent is ten times higher than that occurring in the population at large. The evidence suggests that a relationship exists between the maternal rubella and the development of congenital anomalies.

Also presented are three instances in which virus infection occurred in the ninth month of pregnancy and the children were normal. It is suggested that the virus infection must occur during early pregnancy in order to produce a congenital anomaly. The authors quote Goodpasture, who suggested that young, relatively undifferentiated cells are more easily affected by the virus than mature cells. BELLET.

Ash, R.: Precordial Leads in Childhood; Comment on the Presence of Double Upward Deflections in Leads From the Sternal Region of Normal Children. Am. J. Dis. Child. 70: 277 (Nov.-Dec.), 1945.

This study analyzes single tracings obtained from 150 children whose electrocardiagraphic examination included precordial leads (CF_2 and CF_4). The children ranged in age from 9 days to 15 years, the average being 7.6 years and the age of greatest frequency being 8 years. The most striking variation from the electrocardiogram of an adult was in the T waves, which were usually inverted in leads near the sternum, but were also not infrequently inverted in leads in the region of the apex. The frequency of inversion diminished with the increased age of the child, depending on the age of the child and the position of the electrode on the chest wall. Negative, diphasic, or positive T waves may therefore be normal in childhood.

A P wave of amplitude greater than 2 mm. in Lead CF_2 or 1 mm. in CF_4, whether upright, diphasic, or inverted, or a duration greater than 0.08 second was considered abnormal.

The presence of a Q wave in CF_2 was considered abnormal. In CF_4 the presence of the Q wave less than 25 per cent of the amplitude of the R wave probably has no significance. An absent R wave or one smaller than 1 mm. in either lead was considered abnormal.

Triphasic complexes (double upward deflection) and M-shaped QRS complexes have been described as always abnormal in Leads CF_2 and CF_4. Ash observed that in normal children, triphasic complexes may be observed in the region to the left of the sternum. Such complexes were considered abnormal in only six children in whom the transient nature of the distortion seemed proved by the presence of diphasic complexes in subsequent tracings. In this group, four children suffered from rheumatic fever and two suffered from hemorrhagic nephritis.

An S-T segment deviation greater than 2 mm. above or 1 mm. below the isoelectric line was considered abnormal.

A T wave greater than 8 mm. in amplitude in CF_2 or CF_4 or an inverted T wave greater than 8 mm. in Lead CF_2 or 6 mm. in Lead CF_4 was considered abnormal.

The presence of features in the electrocardiograms of normal children which would be interpreted as abnormal in adults necessitates the use of caution in the interpretation of a single electrocardiogram obtained from one or more precordial positions in childhood. However, after rheumatic fever children not infrequently show abnormal changes in the precordial leads which are not present in limb leads and these changes present an additional clue to the presence of myocardial damage. BELLET.

Rantz, A. L., Spink, W. W., and Boisvert, P. J.: Abnormalities in the Electrocardiogram Following Hemolytic Streptococcus Sore Throat. Arch. Int. Med. 77: 66 (Jan.), 1946.

Detailed serial electrocardiographic studies were made in 185 patients with acute hemolytic streptococcic disease of the respiratory tract, approximately 50 of whom exhibited signs of an arthritic or nonarthritic continuing disease. Definite electrocardiographic abnormalities were observed in 31 of these patients. Twenty-two patients belonged to the nonarthritic group. This group manifested significant prolongation of the P-R interval in 15 patients and T-wave changes in seven patients. The abnormalities persisted from three to twenty-eight days. Of the group of patients who had gonorrhea with arthritic manifestations, five showed conduction disturbances and four showed T-wave changes. Arthritic poststreptococcic disease was more severe than the nonarthritic type. The presence of these electrocardiographic changes was invariably associated with other evidence of a continuing abnormal tissue reaction, as manifested by elevated sedimentation rate, fever, malaise, or arthritis. The authors emphasize that the abnormalities of the electrocardiogram of the type observed in their study during the poststreptococcic state may also be observed during and after attacks of other infectious diseases, such as typhoid, typhus, gonococcic arthritis, pulmonary tuberculosis, malaria, rheumatoid arthritis, and lobar pneumonia. They suggest that the frequency, duration, and magnitude of the abnormality will be greater after an infection by hemolytic streptococci, but that true specificity of the changes observed cannot be established. It is concluded that the manifestations which follow acute hemolytic streptococcic infection of the respiratory tract are similar to those of rheumatic fever, that the type of poststreptococcic continuing disease with arthritis is a tissue reaction identical with that ordinarily described as rheumatic fever, and that the nonarthritic illness is a closely related process. BELLET.

Hartz, P. H., and Van der Sar, A.: Occurrence of Rheumatic Carditis in the Native Population of Curacao, Netherlands West Indies. Arch. Path. 41: 32 (Jan.) 1946.

There is a widely accepted belief that acute rheumatic fever and rheumatic carditis are extremely rare or actually nonexistent in the tropics. Opinion in this regard is unreliable, however, when it is based on clinical observation alone. Only when autopsies and careful histologic examinations have been made in relation to a known sample of the population can conclusions as to the incidence of these diseases be considered valid. In a controlled study, it was found that among 3,391 medical admissions to a hospital in Curacao, Netherlands West Indies, during a period of five years, there were 61 patients who had acute rheumatic fever and three patients who had chorea. No cases of scarlet fever were observed. Among 1,307 autopsies on natives of Curacao, Aruba, and Bonaire, typical gross lesions of rheumatic carditis were found in 20 cases. Histologic examination was made in 12 of these cases, and in 11 instances Aschoff lesions were identified.

Rheumatic fever is certainly more frequent in the tropics than is commonly believed. There is a need for more reliable data on the subject, especially for autopsy studies with histologic examination. LAPLACE.

Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis With Penicillin. Ann. Int. Med. 24: 170 (Feb.) 1946.

The authors present 15 new cases of subacute bacterial endocarditis treated with penicillin in addition to the follow-up of 17 of the 20 cases which they previously reported. Of the 35 patients, 30 are alive and apparently cured of the infection. The average period of follow-up has been fourteen months.

Their method of treatment consisted of continuous intramuscular drip for eight to twenty-seven days. A twenty-four-hour volume of 250 to 500 c.c. of penicillin solution in 0.85 per cent sodium chloride was well tolerated. Repeated courses were necessary in some cases, with increased dosage and/or length of time, depending on the sensitivity of the individual organisms to penicillin. No relapses occurred later than two weeks after treatment. In no case did the infecting organism develop significant resistance to penicillin. Two patients died but culture at post-mortem examination revealed no active infection.

The authors discuss the role of heparin in this disease and believe that it is of doubtful value except in special circumstances. A table is given for the correlation of penicillin serum levels with twenty-four-hour dose. They feel that it is advisable to maintain a serum level of penicillin at least four times as high as the amount required to inhibit the growth of the organism in vitro. If this information is not available, they recommend a trial of 500,000 units by this method daily for two to three weeks. If unsuccessful, recourse to an appropriately equipped laboratory becomes imperative. M. W. STROUD.

Scherlis, S.: The Recognition and Clinical Significance of Auricular Heart Sounds. Ann. Int. Med. 24: 254 (Feb.) 1946.

The author discusses the difference between presystolic "murmurs" and presystolic "sounds" confusion in this regard may lead to a mistaken diagnosis of heart disease. Auricular sounds are usually obscured by the normal first heart sound but may be heard as a low-pitched sound in diastole in cases of A-V dissociation. The mechanism by which the two parts of the auricular sound are produced is discussed. The first part can be heard more easily in children, while the second part is heard in some cases of heart block. Auricular sounds have been noted clinically in patients with hypertension, sickle cell anemia, hyperthyroidism, and Besnier-Boeck-Schaumann disease without evidence of cardiac disease. Split first sounds at the apex are usually of equal intensity while an auricular component is softer and lower pitched than the ventricular component.

The mechanism of the Austin-Flint murmur of aortic insufficiency is said to be due to blood regurgitating through a damaged aortic valve against the anterior mitral curtain and pushing it into the blood stream passing from auricle to ventricle. The presystolic murmur of mitral stenosis is dependent upon effective auricular contraction but may be present in fast auricular fibrillation due to a summation of the mid-diastolic murmur and the normal first sound with shortening of diastole.

The importance of the left lateral position of the body to bring out sounds is noted and the simultaneous use of electrocardiogram, stethogram, and jugular pulse is illustrated to clarify the discussion. M. W. STROUD.

Sensenbach, W., and Buie, R. M., Jr.: Persistent Ventricular Bigeminal Rhythm in Apparently Normal Hearts. Am. J. M. Sc. 211: 332 (March) 1946.

In a series of 33 patients presenting bigeminal rhythm, eight patients were observed in whom evidence of heart disease was lacking but who had frequent regularly occurring premature beats. Four of these patients presented evidence of advanced arteriosclerosis so that heart disease could not be entirely excluded. In the remaining cases, occasional short periods of bigeminal rhythm were present in two women in whom profound emotional factors were found to be operative.

The two remaining cases of persistent bigeminal rhythm were observed in a 12-year-old mentally deficient girl and in a 33-year-old woman with rheumatoid arthritis, associated with marked emotional disturbance related to the skeletal deformity and the incapacity caused by the arthritis.

The cause for the occasional occurrence of persistent bigeminal rhythm with apparently normal hearts is unknown. BELLET.

Starr, I., and Friedland, C. K.: On the Cause of the Respiratory Variation of the Ballistocardiogram, With a Note on Sinus Arrhythmia. J. Clin. Investigation 25: 53 (Jan.) 1946.

Ballistocardiographic impacts increase in size during inspiration and decrease in size during expiration. Evidence is presented showing that this variation is due to changes in pressure rather than to changes in the heart's position. It is impossible to reverse the respiratory effects upon the ballistocardiogram by changing the subject's position on the table. Inflation of the lungs by a blast of air is capable of reversing this respiratory variation even though the heart's axis is brought closer to the axis of the recording instrument by the

diaphragmatic descent thus produced. Breathing through an obstruction and thus exaggerating the pressure differences of the cycle without influencing the changes of the heart's position greatly increases the respiratory variation of impacts. In a patient with an aneurysm of the left ventricle it was demonstrated that the right ventricle's contribution to the ballistocardiogram is greater than that of the left ventricle during inspiration and is less than that of the left ventricle during expiration. These relationships can be reversed by inflating the lungs with a blast of air. It is apparent that blood is sucked into the chest during inspiration thus enhancing right ventricular filling; left ventricular filling is diminished during inspiration owing to the increased quantity of blood contained in the expanded lungs. During expiration less blood flows into the chest and right ventricular filling is accordingly reduced whereas left ventricular filling is enhanced by the blood being "squeezed" out of the pulmonary reservoir. Records of arterial pressure obtained by means of the Hamilton manometer support this thesis in that arterial pressure declines during inspiration and rises during expiration. Sinus arrhythmia is related to reduced right ventricular filling during expiration: the heart behaves as if it were waiting for the right ventricle to be filled before contracting. FRIEDLAND.

Elkinton, J. R., Danowski, T. S., and Winkler, A. W.: Hemodynamic Changes in Salt Depletion and in Dehydration. J. Clin. Investigation 25: 120 (Jan.) 1946.

Acute salt depletion in dogs produces a shocklike state resembling traumatic shock. There is a reduction in cardiac output, plasma volume, circulating plasma protein, blood pressure, circulation rate, and extracellular fluid volume. Water-depleted animals that have a comparable diminution in extracellular fluid volume do not display peripheral vascular collapse although cardiac output, plasma volume, mean arterial pressure, and circulation rate may decline. The hemodynamic differences between salt and water depletion may be related to complete maintenance or very slight reduction in the circulating plasma protein in the latter. The importance of salt depletion as a precursor of the shocklike state in untraumatized animals is emphasized. FRIEDLAND.

Wiggers, H. C., and Ingraham, R. C.: Hemorrhagic Shock: Definition and Criteria for Its Diagnosis. J. Clin. Investigation 25: 30 (Jan.) 1946.

Hemorrhagic shock was produced in dogs by rapid bleeding from a femoral artery until the mean arterial blood pressure fell to 40 mm. of mercury. This level was maintained for ninety minutes by additional bleeding as needed and all the blood withdrawn was reinfused at the end of this period. A classification for the shock thus produced is proposed: (1) simple hemorrhagic hypotensive state in which the blood loss does not exceed 40 per cent of the total blood volume and from which the animal usually recovers by means of his inherent compensatory regulatory mechanisms; (2) impending shock state where the blood loss exceeds 40 per cent of the total circulating blood volume and from which the animal may recover if it is infused with suitable agents; and (3) irreversible shock state from which the animal does not recover despite infusion of suitable agents. Five criteria for the adequate diagnosis of the irreversible shock state are proposed: (a) spontaneous arterial pressure decline below 40 to 45 mm. Hg despite attempts to restore the blood pressure to "standard" hypotensive level by means of infusions of saline or whole blood; (b) relative hemoconcentration during the hypotension period [an unfavorable prognosis is indicated when the plasma specific gravity declines to a static level within the first sixty minutes of the hypotensive period; an even more unfavorable prognosis is indicated should plasma specific gravity begin to rise (after the initial decline) before the termination of the ninety-minute hypotensive period]; (c) diarrhea and passage of blood-tinged fecal material following the termination of the ninety-minute hypotensive period; (d) postreinfusion heart rate of 150 beats per minute despite normal blood pressure, indicating a state of irreversible shock; and (e) postreinfusion blood or plasma specific gravity which is likely to be higher than the control value in the animals that die whereas in surviving animals it is likely to be less than the control value.

FRIEDLAND.

Book Reviews

VALOR PRONOSTICO DEL ELECTROCARDIOGRAMA. By M. Vela, M.D., Libreria Edit., Cient. Med. Esp., Madrid, Spain, 1944. Vol. 1 contains 336 pages with 252 illustrations, and Vol. 2 contains statistical data.

This work deals with the prognostic value of electrocardiography, a fascinating but extremely difficult problem.

The first part is devoted to an historical review. The second discusses the material on which the writer's work is based, namely 11,000 ambulatory patients. The third part discusses the prognosis for each wave pattern and for each electrocardiographic diagnosis. The fourth part discusses the mode of death and the age at death in different diseases.

The work is based on the study of two different tables. One of them lists the frequency of each electrocardiographic sign in the different diseases and its respective mortality. The other lists the mortality of each disease without considering the electrocardiogram. A comparison is then made between the mortality of a disease and that of the same disease when a certain electrocardiographic abnormality is present.

The relatively short duration of life of the patients (43 per cent of patients with mitral stenosis died within three years) indicates that they were examined for the first time when the clinical course was well advanced, a fact which lessens the interest of some of the data.

Among the results of the study, the following deserve mention: (1) Bundle branch block has a very high mortality, 68 per cent. (2) Inversion of T in Leads I and II has a 60 per cent mortality; T-wave inversion in Leads II and III has only a 47 per cent mortality. (3) Inverted T_3 with right axis deviation has a mortality of 64 per cent; inverted T_3 with left axis deviation may be normal. Left axis deviation with upright T may be a serious abnormality. (4) Sudden death cannot be foreseen on the basis of electrocardiographic tracings. (5) Patients with a normal electrocardiogram have a better prognosis than otherwise, whatever the disease.

Some of these and other conclusions may seem unexpected. This is partly due to the fact that one cannot correlate the electrocardiographic abnormality with the other clinical data, and partly to the inherent weakness of all statistical studies: their dependence on the method and material employed.

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